Limb Salvage and Recovery After Blast-Related Injury

Proceedings and Expert Findings from a U.S. Department of Defense International State-of-the-Science Meeting

TEPRING PIQUADO, EMILY HOCH, CHARLES C. ENGEL

Prepared for the U.S. Army Medical Research and Development Command
Approved for public release; distribution unlimited

RAND NATIONAL DEFENSE RESEARCH INSTITUTE

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Preface

This document represents the complete proceedings of the Eighth Department of Defense (DoD) International State-of-the-Science Meeting (SoSM) for Blast Injury Research, held March 5–7, 2019, at the RAND Corporation's Arlington, Virginia, office. The SoSM topic was "Limb Salvage and Recovery After Blast-Related Injury." The SoSM aims to identify knowledge gaps in blast injury research; ensure that DoD medical research programs address existing gaps; foster collaboration between scientists, clinicians, and engineers in blast injury–related fields; promote information sharing on the latest research; and identify immediate, short-term, and long-term actions to prevent, mitigate, and treat blast injuries. Participants and presenters included scientists, clinicians, and policymakers from DoD, including the Departments of the Army, Navy, and Air Force; the Marine Corps; the National Institutes of Health; and the U.S. Department of Veterans Affairs (VA); as well as representatives from academia and industry and scholars from several different countries.

These conference proceedings provide summary information on (1) the background of the meeting, (2) the systematic literature review that RAND researchers completed in support of the meeting, (3) the meeting keynote address, (4) all meeting presentations and abstracts, (5) working group findings, and (6) SoSM conclusions and recommendations. These proceedings will be of particular interest to scientists, clinicians, military personnel, and policymakers working in areas related to military medicine and health, blast injuries, traumatic limb injuries, and, of course, limb salvage.

The Human Subjects Protection Committee (HSPC) is RAND's institutional review board (IRB) to review research involving human subjects, as required by federal regulations. RAND's Federalwide Assurance for the Protection of Human Subjects (FWA00003425, effective until July 1, 2018) serves as the organization's assurance of compliance with the regulations of 17 federal departments and agencies. According to this assurance, the HSPC is responsible for review of all research, regardless of the source of funding. The views of sources used in this study are solely their own and do not represent the official policy or position of DoD or the U.S. government.

This research was sponsored by the DoD Blast Injury Research Coordinating Office (BIRCO) and conducted within the Forces and Resources Policy Center of the RAND National Defense Research Institute, a federally funded research and development center sponsored by the Office of the Secretary of Defense, the Joint Staff, the Unified Combatant Commands, the Navy, the Marine Corps, the defense agencies, and the defense intelligence enterprise.

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Acknowledgments

The RAND National Defense Research Institute (NDRI) team of researchers gratefully acknowledges Michael Leggieri, Dr. Raj Gupta, and COL Sidney Hinds of the Blast Injury Research Coordinating Office (BIRCO) for their comments, guidance, and support for this project. Thanks also go out to the members of the planning committee of the Eighth Department of Defense International State-of-the-Science Meeting (SoSM) on Blast Injury Research (see Appendix F). These individuals helped the research team identify and rank candidates for the expert panel, advised on invited speaker topics, nominated invited speakers, peer-reviewed submissions for the SoSM abstract, provided input to SoSM working group discussion questions, helped refine the SoSM agenda, and moderated the SoSM question-and-answer panels.

The RAND team derived inspiration, support, and collaboration from the expert panel of the SoSM. Each expert panelist chaired a daylong SoSM participant working group. Key parts of this document (findings, conclusions, and recommendations) were written in close consultation with these respected scholars:

- Rory A. Cooper, Ph.D., Paralyzed Veterans of America Distinguished Professor of Rehabilitation Science and Technology and Orthopedic Surgery at the University of Pittsburgh in Pittsburgh, Pennsylvania; VA Senior Research Career Scientist at the Human Engineering Research Laboratories at the University of Pittsburgh
- Barbara Springer, P.T., Ph.D., research physical therapist at the Henry M. Jackson Foundation for the Advancement of Military Medicine, Center for Rehabilitation Sciences Research, Department of Rehabilitation, Walter Reed National Military Medical Center in Bethesda, Maryland
- Alberto Esquenazi, M.D., chair of the Department of Physical Medicine and Rehabilitation at Albert Einstein Medical Center in Philadelphia, Pennsylvania; professor of physical medicine and rehabilitation at the Jefferson University School of Medicine in Philadelphia, Pennsylvania; and professor of biomedical engineering at Drexel University
- Douglas Smith, M.D., professor at the Department of Rehabilitation Medicine; Henry M. Jackson Foundation for the Advancement of Military Medicine's chief orthopedic adviser for the Center for Rehabilitation Sciences Research, Uniformed Services University of the Health Sciences in Bethesda, Maryland
- Joseph R. Hsu, M.D., professor of orthopedic trauma at Carolinas Medical Center in Charlotte, North Carolina; and director of the Limb Lengthening and Deformity Service and vice chair of quality at the Atrium Health Musculoskeletal Institute in Charlotte, North Carolina

- James Ficke, M.D., F.A.C.S., Robert O. Robinson Professor of Orthopaedic Surgery and director of the Department of Orthopaedic Surgery at Johns Hopkins School of Medicine in Baltimore, Maryland.

The RAND team also included additional staff in the RAND Corporation's Arlington, Virginia, office. Notetaking support was provided by Kofi Amofa, Melissa Shostak, Sarah Fieldhouse, Katrina Doss-Owens, Cedric Kenney, and Mary Kate Adgie; and project administrative assistance was provided by Lee Remi. Finally, the RAND team thanks Craig Bond, Samantha McBirney, Paul Steinberg, and Emily Ward for reviewing and commenting on these conference proceedings.

Abbreviations

4AP	4-aminopyridine
BMP	bone morphogenetic protein
BOP	blast overpressure
CFU	colony-forming units
COP	chondro-osseous progenitor
CP	cyclophosphamide
dHACM	dehydrated human amnion/chorion membrane
DoD	U.S. Department of Defense
DTIC	Defense Technical Information Center
fLS	flap-based limb salvage
FDA	Food and Drug Administration
HET OSS or HO	heterotopic ossification
IED	improvised explosive devices
IDEO	Intrepid Dynamic Exoskeletal Orthosis
LEAP	Lower Extremity Assessment Project
METRC	Major Extremity Trauma Research Consortium
METALS	Military Extremity Trauma Amputation/Limb Salvage
MSKI	musculoskeletal injuries
NIH	National Institutes of Health
O	osteoblast
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
PEG	polyethylene glycol
PM&R	physical medicine and rehabilitation
PT	physical therapy
PTSD	posttraumatic stress disorder
Q&A	question and answer

SoSM	State-of-the-Science Meeting
teLS	tissue engineering limb salvage
TPNI	traumatic peripheral nerve injury
USAMMDA	U.S. Army Medical Materiel Development Activity
USUHS	Uniformed Services University of the Health Sciences
VA	U.S. Department of Veterans Affairs
VAC	vacuum-assisted closure
VAVIS	VA Vascular Injury Study
WRAIR	Walter Reed Army Institute of Research

CHAPTER ONE

State-of-the-Science Meeting Summary

During the conflicts in Iraq and Afghanistan, there have been changes in the mechanism, severity, and complexity of injuries from improvised explosive devices (IEDs)—changes that have resulted in a higher incidence of combat-related traumatic injuries. Battlefield medical advances and improvements in protective equipment have resulted in a greater proportion of blast-exposed service members surviving their severe injuries, and progress in surgical reconstruction and rehabilitation has resulted in an increased medical capacity to salvage limbs, despite the severe injuries. Collectively, these developments have led to important questions about when to emphasize limb salvage over other treatment options—most notably, amputation—for individuals with severe blast-related limb injuries.

The theme of the Eighth Department of Defense International State-of-the-Science Meeting (SoSM) on Blast Injury Research was "Limb Salvage and Recovery After Blast-Related Injury" and was intended to help address these questions. The meeting was held March 5–7, 2019, at the RAND Corporation's Arlington, Virginia, office. The objectives of the SoSM meeting were as follows:

1. Describe the epidemiology and outcomes of limb salvage after severe blast-related limb injury.
2. Review the evidence on the decision to salvage versus amputate a limb after severe blast-related limb injury.
3. Examine the evidence and innovations on restoration and reconstruction after limb salvage for severe blast-related limb injury.
4. Review the evidence and innovations on rehabilitation, reintegration, and recovery after limb salvage for severe blast-related limb injury.

More than 120 scientists, clinicians, and military leaders from related fields provided scientific overviews, presentations, and posters describing new and emerging science. Before the meeting, a conference-planning committee invited a panel of six leading scientists and clinicians in related fields to serve as an expert panel, lead working groups, and develop overall recommendations.

This document represents the complete proceedings of the eighth SoSM. Supporting appendixes provide a list of previous SoSMs (Appendix A); the eighth SoSM agenda (Appendix B); biographies of the keynote speaker (Appendix C), invited speakers (Appendix D), and expert panelists (Appendix E); and lists of the planning committee members (Appendix F) and attendees (Appendix G).

The eighth SoSM was the latest meeting in a series established in 2009 under the authority of the U.S. Department of Defense (DoD) Executive Agent for Blast Injury Research, sponsored by U.S. Army Medical Research and Development Command (USAMRDC) and the DoD Blast Injury Research Coordinating Office (BIRCO). The series aims to identify knowledge gaps in blast injury research; ensure that DoD medical research programs address existing gaps; foster collaboration between scientists, clinicians, and engineers in blast injury–related fields; promote information sharing on the latest research; and identify immediate, short-term, and long-term actions to prevent, mitigate, and treat blast injuries. See Appendix A for a list of previous SoSMs and their themes.

Questions and Answers

Working groups developed responses to five questions designed in advance of the SoSM to address the four meeting objectives.

1. How big is the problem of severe blast-related limb injury? What research is needed to better characterize the magnitude of this problem?

Each working group agreed that defining *limb salvage* is complex and requires a classification system that is reproducible, reliable, and valid. A working definition should (1) be capable of evolving over time, (2) include maintaining as much limb function as possible, and (3) indicate that patients with amputations can also be considered patients with limb salvage. Once a definition is agreed upon, the coding system must be updated to encompass salvage diagnoses, procedures, and outcomes from point of injury through rehabilitation.

The magnitude of the problem can be defined by quantity, such as the number of patients affected or the detriment to the force, or by outcomes, such as quality of life or limb function. Military and civilian Level 1 trauma center records should be mined to develop a minimum data set. In time, international data can be incorporated, such as data from low-income countries with high incidence rates and poor tracking. Researchers should consider whether the problem will be the same in the future or change as the nature of warfare evolves.

2. What factors figure into the immediate and ongoing decision to salvage versus amputate a limb after severe blast-related limb injury? What research is needed to better guide this decision?

Many physical and psychosocial factors figure into the immediate and ongoing decision to salvage versus amputate a limb after severe blast-related limb injury. Physical factors include pain, which tissues were injured, severity of the injury and comorbidities, cosmetic concerns, age, overall health, and fitness. Psychosocial factors include length of recovery time, clinical experience, quality of life, availability of rehabilitation services and technology, and resource constraints. To better guide this decision, each working group recommended a long-term prospective study on costs, healthcare utilization, and quality of life. Decision pathways and scoring systems for muscle, vascular, bone, skin, and nerve status would aid consistent clinical decisionmaking. In addition to prospective studies, retrospective studies correlating factors with outcomes of limb-salvage patients, Delphi studies of clinicians and patients on decisionmaking, or analyses of the DoD Trauma Registry can be used. Longer-term research predictors and biomarkers should incorporate the needs of salvage patients.

3. What are the most promising innovations for restoring and reconstructing a salvaged limb after severe blast-related limb injury? What research is needed to understand their effectiveness and limitations? What outcomes should be studied?

To counter tissue loss and default decision to amputate, new technologies to stabilize and preserve tissue are needed. Wound dressings need to prevent necrosis, infection, and dehydration. Working groups urged development of a new vacuum-assisted closure (VAC) of a wound, which can monitor the affected limb while preventing compartment syndrome and infection and maintaining oxygen saturation. Research into new interventions is complex because of a heterogenous population and the low incidence outside conflict. Experts recommended testing Food and Drug Administration (FDA)–approved interventions; drawing on research in similar areas, such as genetic bone disorder; and looking at restoration of body function through external technology, such as exoskeletons, and biofeedback devices, such as wearable devices.

Outcome measures can be borrowed from amputation studies and should be adopted universally by military treatment facilities (MTFs) and U.S. Department of Veterans Affairs (VA) hospitals. These measures should include patient-reported outcomes, function, physical activity, ability to return to work, costs, and a psychological assessment. Experts emphasized that a high level of function should be the desired outcome and that any follow-on surgeries should aim for a meaningful gain in function.

4. What are the most promising rehabilitative innovations after limb salvage for severe blast-related limb injury? What research is needed to understand their effectiveness and limitations?

Innovations were divided into *technological*, *therapeutic*, *patient-centered*, and *regenerative*. Technological innovations improve functional capabilities and can include, for example, Intrepid Dynamic Exoskeletal Orthosis (IDEO) devices, implantable and wearable orthotics, and devices providing haptic feedback to portions of the salvaged limb that retain sensation. Technological innovations also can include *in vivo* additions, such as 4-aminopyridine (4AP) or stem cell therapy for tissue repair. Therapeutic innovations incorporate comprehensive rehabilitation that includes psychosocial impacts and pain management. Patient-centered innovations can improve rehabilitation outcomes with motivational devices, such as smart watches. Regenerative techniques integrate technology with therapeutic innovations.

Experts agreed that rehabilitation is poorly tracked. Research must examine dosing, intensity, and timing of rehabilitation protocols with greater granularity of specific exercises. Research should be holistic and incorporate nutrition, pain management, and mental health outcomes. Furthermore, studies should consider what can be done before patients arrive at the rehabilitation clinic, such as reducing muscle degeneration, bracing, and providing psychological support.

5. What are the most important research, technology, and policy opportunities and gaps pertaining to limb salvage after severe blast-related limb injury?

In the short term, standardizing and implementing a shared definition of *limb salvage* was considered essential. Doing so will provide a systematic way to categorize and quantify the injuries to allow for outcomes research. Ideally, prolonged field care and en-route care efforts should be correlated with short- and long-term treatment outcomes. Because these injuries are, fortunately, rare, real-time telementoring and civilian consults can ensure that there will be a suf-

ficient workforce capable of treating these injuries. A clinical center of excellence will promote a culture of limb salvage to facilitate the collection of best practices.

In the medium to long term, researchers should develop algorithms to provide feedback to clinicians and patients on the probability of successful salvage. As surgical and rehabilitation techniques are approved, decisionmakers should consider how military culture affects decisions to salvage versus amputate limbs. Longer-term research can look to bone growth, nerve regeneration, and muscle regeneration.

Responses to these questions, provided in these proceedings, were informed by participant presentations and the expert panelist–led working groups. (See Appendix E for biographies of expert panel members and Appendix G for meeting participants.) The working groups identified and prioritized unresolved challenges and recommended short-, medium-, and long-term actions and directions. Following the meeting, the expert panel developed the following DoD research and policy findings and recommendations about limb salvage and recovery after severe blast injury.

Discussion and Recommendations

There is a very limited body of empirical research on blast-related injuries to extremities and subsequent limb salvage, and much more research is needed. The following are the recommendations from the expert panel.

1. Write an Agreed-Upon Definition of *Trauma-Related Limb Salvage*, and Disseminate It to the Professional Societies Representing Injured Service Members

Discussion

Within the field, there is a varied use of the term *limb salvage*. Experts do not explicitly define the term; instead, limb salvage is referred to as "not an amputation," "limb restoration," or "limb-sparing," or these terms are used interchangeably. Limb salvage is also described in terms of procedures, such as involving either local or free muscle flaps or microvascular free-tissue transfer for wound coverage, management of vascular injuries, operative treatment and revascularization, bone grafting or bone transport, repair of a major nerve injury, treatment of a complete compartment injury or compartment syndrome, and plastic-surgical techniques.

Recommendations

In the short term, a definition of *trauma-related limb salvage* should be developed, validated, and published. Common elements of the definition should include the following: the agreement that *limb salvage* is the ability to maintain partial structure of the limb or joints, a transition from "major" or "minor" amputation to proximal or distal anatomical descriptors, and a clear concept of what limb salvage is not. Specifically, limb salvage is not an amputation, a transplant, or the total loss of tissue (i.e., the hand at the wrist or the foot at the ankle).

2. Recommend Funding to Support Randomized Controlled Trials of Clinical Care Models and Treatment Studies That Involve Large Civilian-Military Consortia

Discussion

To date, prognostic assessment tools largely have failed as decision aids for clinicians and patients. There is no one-size-fits-all intervention for severe blast-related limb injuries, and

ongoing, intensive efforts to share and study decisionmaking with patients, caregivers (as appropriate), and a multidisciplinary clinical team are needed. Furthermore, there is limited evidence on the outcomes of amputation versus limb salvage overall and in clinically relevant subgroups.

Recommendations

Assemble interdisciplinary study sections with experts who are knowledgeable about rehabilitation interventions, outcome measures, and limb salvage. Establish joint DoD-civilian Level 1 trauma centers to enroll civilians in prospective trials.

3. Increase Transparency of Rehabilitation Practices to Develop Evidence-Based Recommendations

Discussion

Current evidence comparing various surgical approaches to limb salvage for blast-related limb injury has been limited. As new limb-salvage techniques are developed, appropriately designed controlled trials could aid in the examination of the effectiveness of these techniques.

Recommendations

Physical and occupational rehabilitation should be transitioned to a cohort-based model built on the principles of peer mentoring and successful programs, such as the Center for Intrepid's Return to Run Clinical Pathway for Limb Salvage. Joint limb salvage and amputation MTF centers of excellence should be established. These centers might break down the traditional silos between the physical therapy and occupational therapy communities, as well as those between different parts of the anatomy. An external body should review the mission and effectiveness of the centers, as well as the VA and the Extremity Trauma and Amputation Center of Excellence (EACE), ensure that best practices are shared, and ensure that high-quality limb-salvage and amputation care is being conducted.

4. Improve Physical Support Systems for Limb Salvage

Discussion

The most underdeveloped area of empirical research that the RAND team reviewed pertained to rehabilitative approaches to the care of blast-injured patients with severe limb injuries. Promising programs have been identified, but codification and empirical evaluation are needed. Physical support systems for limb salvage have fallen behind prosthetics.

Recommendations

Advances in orthoses, bracing, exoskeletal systems, and robotic-assisted therapies applicable to limb salvage should be prioritized. Prospective trials should be designed to evaluate comparative effectiveness of rehabilitation interventions. New or revised measures of functional, subjective, quality-of-life, psychosocial, and patient-recorded outcomes must accompany these trials. Researchers must be clear about which outcomes they are measuring and which tools are appropriate. Currently, no validated tool measures the wide range from minimal function to return to duty, nor are there comparative measures between amputation and limb salvage. Additionally, researchers should study the effects of adaptive reconditioning to elevate the median expectations of limb-salvage patients. Clinical practice guidelines should reflect these changes from training to the battlefield. The shortage of trained surgeons should be bolstered by real-time telementoring and civilian consults.

Overall, the National Institutes of Health (NIH) and other funders should revisit how they fund research on limb salvage. The NIH should stand up a special study section specific to total care with a focus on comparative effectiveness, including researching proper timing and dosage. Historically, these studies have scored lower and have not been funded because of the lack of strong outcome measures. Embedding scientists in clinical settings and reviewing salary caps of physician scientists also will facilitate shared learning and mentorship.

5. Increase the Pipeline of Trained Surgeons to Serve on the Front Line

Discussion

The shift toward a prolonged field-care scenario highlights significant and concerning gaps for limb salvage. The military currently is unprepared for this operating environment for many reasons, including a lack of trained surgeons to serve on the front line and insufficient training for field medics, focusing more on resuscitation and stabilization and less on surgical care or anesthesia methods. Soldiers cannot stay on the battlefield injured and expect positive outcomes.

Recommendations

Two options offer potential ways forward: (1) Medics are trained as paramedics, and special forces medical sergeants (18 Delta) are trained as physician assistants, or (2) rapid-evacuation technologies are developed and deployed. However, transitioning surgical procedures and administration of anesthesia to field care raises safety and ethical considerations. Supportive technologies, such as a new generation of wound VAC therapy, could reduce contamination, stabilize existing tissue, preserve viability of limbs, and manage pain. Although unmanned aerial vehicles, augmented reality, and real-time audio and visual communication with split surgical teams show promise, most operating environments do not have sufficient bandwidth for consistent connections.

CHAPTER TWO

Literature Review Summary

Background

During the conflicts in Iraq and Afghanistan, there have been important changes in the mechanism, severity, and complexity of blast-related battlefield injuries, largely due to the advent and increased enemy combatant use of IEDs. Although explosive blast in the theater of combat operations is not new, the rise in IEDs has changed the nature of extremity injuries, resulting in more-frequent blast-related physical injuries among deployed service members and more-regular need for acute medical responses directed toward life-threatening complications associated with these injuries. Blast exposures create wide bone and tissue injury not seen in other types of extremity injuries. Furthermore, blast-related bone injuries may not result in the typical types of fractures that orthopedic surgeons are accustomed to seeing (Keeling et al., 2010; Owens et al., 2007).

In addition, military medical advances and improvements in protective equipment have led to greater survival, despite severe blast-related injuries. Hidden explosives—such as IEDs, landmines, and booby traps—are to blame for as many as half of the injuries seen in field hospitals (Ramasamy et al., 2009). The majority of these injuries are to lower extremities (Balazs et al., 2014). Advances in surgical reconstruction and rehabilitation have resulted in an increased medical capacity to salvage limbs that, until recently, would have been amputated. Collectively, these developments have led to important questions about when and how to emphasize limb salvage after severe blast-related limb injuries.

The DoD Blast Injury Research Coordinating Office (BIRCO) sponsored the eighth SoSM. The goal of this SoSM and associated processes was to identify what is known and not known (knowledge gaps) pertaining to key blast injury–related topics and emerging issues. The topic of this SoSM was "Limb Salvage and Recovery After Blast-Related Injury."

Methods

The RAND team first identified potential search terms to use for both peer-reviewed and grey literature searches. Sources included previous blast injury SoSM literature reviews, terms specifically relevant to blast-related limb salvage and recovery, and associated structured vocabulary used to search the literature databases. A preliminary literature search was then performed, and the results were used to improve the initial search strategy. The RAND team also

asked the expert panel—a multidisciplinary group of authorities on blast-related limb salvage and recovery—to review its initial search terms and provide recommendations for changes.

The RAND team then searched the peer-reviewed and grey literature that describes the occurrence and treatment of military blast-related limb salvage. Specifically, the RAND team searched the peer-reviewed scientific literature on PubMed, Web of Science, and PsycINFO and searched the DoD grey literature on the Defense Technical Information Center (DTIC). The period of interest was calendar year 2008 through calendar year 2018. Additional references were identified that (1) were published prior to 2008 or (2) did not meet inclusion criteria but either represented a seminal article (e.g., the original article describing the Parkland formula for fluid resuscitation among burn patients [Scheulen and Munster, 1982]) or provided context for interpreting the literature.

Key Findings from the Literature Review

Epidemiological Research

Epidemiological studies help characterize the magnitude of the blast-related limb salvage and recovery challenge for the military and common outcomes associated with severe blast-related limb injuries.

A few studies have characterized blast-related injuries, including limb trauma, during the armed conflicts in Iraq and Afghanistan. As noted, hidden explosives—such as IEDs, landmines, and booby traps—are to blame for as many as half of the injuries seen in field hospitals (Ramasamy et al., 2009), with the majority of these being injuries to lower extremities (Balazs et al., 2014). Research from the United Kingdom showed that, among military personnel, 77 percent of people who were injured while deployed had an extremity injury, 11 percent of whom had at least one amputation. Of those individuals with an extremity injury, 33 percent had an upper-extremity fracture, and 67 percent had a lower-extremity fracture. Sixty-nine percent of upper-extremity fractures and 58 percent of lower-extremity fractures were open. This meant that extremity injuries accounted for the vast majority of combat injuries in the United Kingdom. However, this research was not specific to blast-related extremity injuries (Chandler et al., 2017).

Symptoms and functional impairment after severe blast-related limb injury are generally significant, even after substantial periods of rehabilitation. One study of 130 service members evacuated to Brooke Army Medical Center with combat-related extremity trauma assessed pain, sleep disturbance, depression, and anxiety using validated measures at the time of hospital discharge. Among these symptomatic patients, 88 percent met study criteria for significant levels of pain, sleep disturbance, depression, or anxiety; physical functioning and mental health functioning were roughly one and two standard deviations below population norms, respectively (Young-McCaughan et al., 2017). In a case-series analysis of individuals injured during recent military conflicts who had undergone late amputation following limb salvage, poor mental health and dissatisfaction with limb reconstruction each were cited as reasons for undergoing late amputation in the majority of patients (Krueger et al., 2015).

Basic Research

Among animal studies, several used a blast tube to investigate the relationship between skeletal system damage and blast exposure. This research showed that, among rabbits, the endothe-

lium is activated in tissue exposed to blasts, which can affect tissue functionality and long-term outcomes (Spear et al., 2015). Among porcines, cartilage demonstrated chondrocyte death, which is associated with osteoarthritis (Shaw et al., 2017).

There also has been basic science research conducted on animals to investigate surgical techniques that might aid in limb salvage. Ward, Ji, and Corona, 2015, showed that autologous minced muscle grafts can be used to treat volumetric muscle loss, a common problem in orthopedic trauma.

Clinical Research

Major Studies

There are four major studies of limb-salvage treatment outcomes: the Major Extremity Trauma Research Consortium (METRC), the Lower Extremity Assessment Project (LEAP), the Military Extremity Trauma Amputation/Limb Salvage (METALS) project, and the VA Vascular Injury Study (VAVIS). Although these projects are not specifically concerned with blast-related limb salvage and recovery, they are large prospective treatment studies that have shaped much of the scholarly discourse on the topic. In this section, the RAND team summarizes these landmark studies and what is known from these and other treatment research studies.

The **LEAP study** focused on clarifying the decision to amputate or salvage a limb when there was severe lower-extremity trauma. It was a prospective, multicenter, observational study. Part of this research attempted to define characteristics of individuals who sustained these types of injuries, as well as the environment surrounding these injuries and the physical aspects of them. The main finding from this study was that, although two-year outcomes were similar between limb-salvage patients and those who opted for amputation, limb-salvage patients were more likely to be rehospitalized in that two-year period (Bosse et al., 2002). Although the LEAP study provided a large body of data, Higgins, Klatt, and Beals, 2010, stated that the study "failed to completely determine treatment at the onset of severe lower extremity trauma" (p. 238).

The **METALS study** measured function, depression, posttraumatic stress disorder (PTSD), chronic pain, and engagement in sports and leisure activities. The researchers found that patients suffering severe high-energy limb injuries had worse self-reported functional status outcomes than those who had salvaged limbs. They also found that 38.3 percent of patients screened positive for depressive symptoms and 17.9 percent for PTSD (Doukas et al., 2013).

The **METRC study** and **VAVIS** are ongoing and had not produced published results within the period defined for this literature review.

In addition, a retrospective study found that, five years after injury, individuals with vascular limb injury—common among blast-related limb-salvage patients—reported reduced functional status compared with national norms (Scott et al., 2014).

Surgical Approaches

Multiple reviews have covered basic surgical approaches to limb salvage (see Blair et al., 2016), including revascularization, external fixation, and serial wound debridements suitable for reconstruction. The RAND team emphasizes research findings assessing novel approaches to limb salvage.

Free flaps refer to tissue that has been detached and moved from a donor site to a recipient site with blood circulation reestablished at the recipient site. Free flaps are used as a method of soft tissue reconstruction after limb injury. Research shows that latissimus dorsi (or simply

dorsi) flaps were the most commonly used, with a success rate of 95.5 percent (Theodorakopoulou et al., 2016). However, with regard to blast-related limb salvage specifically, free-flap construction is said to be most successful when conducted more than seven days after the injury because blast injuries often have environmental debris in the wound. Traditionally, muscle flaps have been favored over fasciocutaneous flaps; however, recent research has suggested that fasciocutaneous flaps and muscle flaps yield comparable clinical outcomes. Sabino, Slater, and Valerio, 2016, noted that, in the military blast-injury context, fasciocutaneous flaps might be a preferred approach because of the increased likelihood that healthy tissue is found on parts of the body covered by body armor. Muscle flaps, however, remain preferred for reconstruction related to open tibial fractures because studies suggest reduced healing time, infection risk, and necrosis (Sabino, Slater, and Valerio, 2016).

Open knee-extensor injuries are also commonly addressed in combat-related lower limb–salvage efforts. According to Andersen et al., 2014, limited research shows that the mean number of required surgeries was 11 and the mean time to community ambulation was 39 months for open knee-extensor mechanism injuries.

Limb-Salvage Decisions and Decision Aids

Only a few studies relevant to blast-related limb salvage and recovery—none randomized—have compared outcomes of limb salvage with those of amputation. In these studies, individuals who underwent amputation tended to have better short-term mobility outcomes compared with those who underwent limb reconstruction, but differences in long-term functional outcomes did not consistently favor either approach. Pain and surgery complications among amputees versus limb-salvage patients did not consistently favor either approach. Studies generally found no differences between treatment groups with regard to mental health outcomes. The largest differences might be related to cost, with lifetime health care costs projected to be nearly three times higher for amputation than for reconstruction (MacKenzie et al., 2007).

Rehabilitative Approaches

In perhaps the most widely cited study of rehabilitative treatment, those with amputation had better functional outcomes than those who had salvaged limbs (Doukas et al., 2013). A systematic literature review concluded that the Return to Run treatment program coupled with an IDEO "can enable return to duty, return to recreation and physical activity and decrease pain in some high functioning patients" (Highsmith et al., 2016, p. 75). A number of prosthetics—which replace body parts, such as amputated limbs—and orthoses that support or align body parts, particularly in the case of reconstructive limbs, have been developed and improved over time and show promise. Isolating the effects of orthotics and prosthetics is challenging because patients might receive more than one of these over time.

CHAPTER THREE

Keynote Address

Dr. Joseph Caravalho, Jr., president and chief executive officer of the Henry M. Jackson Foundation for the Advancement of Military Medicine, delivered the keynote address to attendees of the eighth SoSM. Caravalho's military career has spanned time as a cardiologist and unit medical advisor and culminated in his appointment as the Joint Staff surgeon at the Pentagon. There, he provided recommendations on a wide variety of medical and readiness issues. (See Appendix C for Caravalho's full biography.)

Caravalho walked the audience through the last 18 years of conflict and its impact on soldier health and readiness. Importantly, he introduced the *golden hour*—a geographically based standard of care that sought to have injured soldiers evacuated within 60 minutes—which required a new medevac deployment strategy. Casualty data from Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) illustrated that the signature wounds of war were shifting to an increasing number of amputations, specifically multilimb amputations. Soldiers who might have died in earlier conflicts were saved, though severely injured. Over the past 50 years, there have been positive outcomes in care for those with amputations. The military should consider prioritizing limb-salvage care to achieve similarly positive results.

Caravalho urged the group to contemplate a whole-person approach to recovery, rehabilitation, and reintegration—one that ingrains physical, mental, and spiritual elements. Limb salvage must be a viable option when people are asking to retain their limbs, and greater attention and greater funding must be devoted to this issue. Caravalho offered to use his bully pulpit to encourage greater partnerships within the U.S. government and other nongovernmental organizations.

CHAPTER FOUR

Invited Speaker Presentation Summaries

This chapter provides summaries of the invited speakers' presentations. The summaries were written from notes taken by the RAND team during the SoSM. See Appendix D for speakers' biographies.

Defining Limb Salvage

Dr. Andrea Crunkhorn, D.P.T. (Extremity Trauma and Amputation Center of Excellence), opened the scientific meeting with a pressing problem: There is no consensus on a definition for *limb salvage*. Without a definition, the size of the population cannot be estimated. This affects patients, who might not receive the same level of attention or financial benefits as other patients; resourcing, in that staffing might not be appropriate for the level of care; and research, where understanding the dimensions of the patient cohort has funding implications. Not only is a definition necessary, but a classification system to grade the degree of salvage and level of function, mobility, and sensation is needed as well. Crunkhorn proposed organizing a virtual working group to agree on common elements of limb salvage that are then validated by experts from subspecialties. Additionally, she noted that there is a need for agreement on whether upper and lower limb salvage can share the same definition.

Overview of U.S. Department of Defense Limb-Salvage Research

LTC Dr. Joseph Alderete, M.D. (Center for the Intrepid), provided a broad overview of the state of limb-salvage research. Alderete identified two primary gaps: one at the point of injury and one on improving outcomes. Soldiers in OIF and OEF have faced weapons designed to enhance lethality and the growing threat of delayed evacuation. Prolonged field care will require advanced understanding of compartment syndrome, infection, and facilitating skeletal support. The gap in senior surgical leadership requires a shared understanding of these issues and questions of appropriate levels of tissue debridement, reliable biomarkers, and future options for remote learning and consultations. Improving outcomes will require investments in bone defects and osseous gaps, neuromodulation, pain management, prevention of late infection, managing volumetric muscle loss, and designing new orthoses.

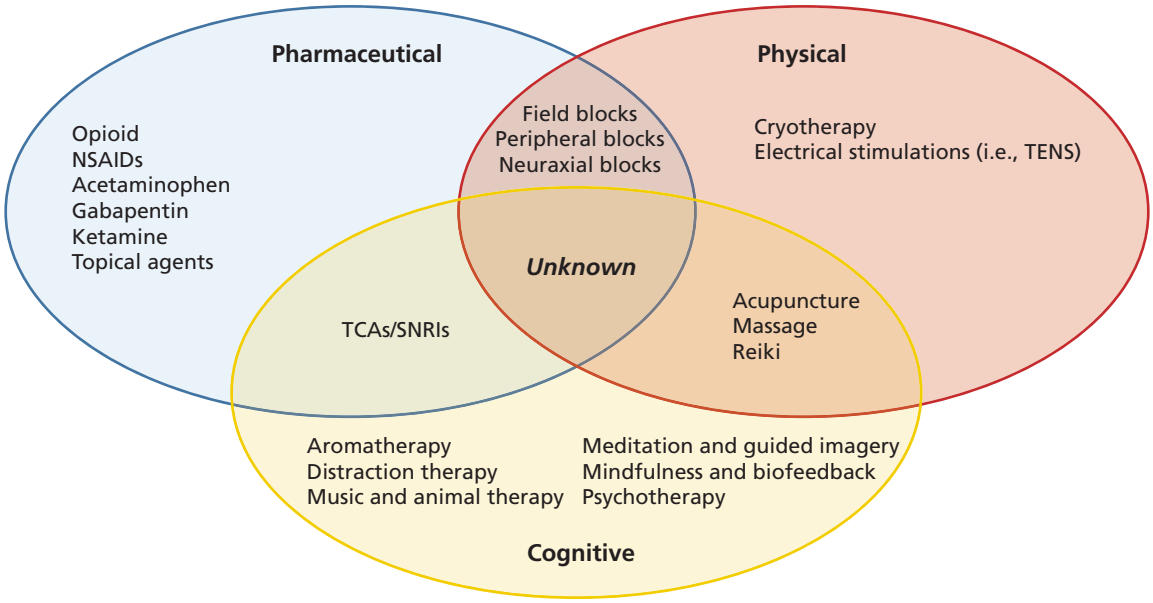
Advances in Surgical Reconstruction

Dr. Joseph Hsu, M.D. (Carolinas Medical Center and Atrium Health Musculoskeletal Institute), urged the group to weigh the balance of short-term successes versus long-term outcomes. For soldiers to overcome the psychological burden of limb reconstruction following salvage, it is critical that they are returned to an active lifestyle. Hsu recommended a whole-patient model in which the entire body is evaluated and there is a focus on preventing infection and alleviating pain. Hsu strongly recommended local delivery for infection management, such as antibiotic-coated implants, which can reduce the risk of complications. Multimodal pain management—comprising pharmaceutical, physical, and cognitive therapies (Figure 4.1)—is a promising technique to alleviate pain and limit the risk of opioid dependence.

Advances in Reconstruction and Restoration Research

LTC(P) Benjamin Potter (Walter Reed National Military Medical Center), summarized recent advances in surgical reconstruction techniques. There is no reliable scoring system to help surgeons determine whether to salvage or amputate a limb. Instead, clinicians need to rely on patient history and injury patterns and assess the state of the patient proximal and distal to the point of injury. General principles for clinicians to follow, in order of importance, are as follows: save the patient's life, save the extremity (if possible; if not, save what can be saved), preserve options for the patient and downstream surgeons, and close injuries in a delayed fashion to limit the risk of infection and acute compartment syndrome. Potter also provided an

Figure 4.1
Multimodal Pain Management



SOURCE: Joseph Hsu, eighth SoSM.
NOTES: NSAID = nonsteroidal anti-inflammatory drug. TENS = transcutaneous electrical nerve stimulation. TCA = tricyclic antidepressant. SNRI = serotonin-norepinephrine reuptake inhibitor.

overview of the current state of external fixation frames, volumetric muscle loss, nerve management techniques, transplants, amputation bionics, rehabilitation, blood flow restriction, orthotic bracing, and the role of precision medicine. Musculoskeletal injuries (MSKI) account for 53 percent of the medically nondeployable population, representing the number-one issue limiting medical readiness. Potter argued that using such data-driven approaches to MSKI outcomes as the Military Orthopaedics Tracking Injuries and Outcome Network (MOTION) could return up to 10 percent of these soldiers to deployment-ready status.

Advancing Technology for People with Limb Salvage

Dr. Rory Cooper, Ph.D. (University of Pittsburgh and U.S. Department of Veterans Affairs), shared the current state of assistive technology for people with limb salvage, for amputees, and for those with other physical limitations. Because service members will eventually shift to civilian life, veteran transition programs need to understand military, veteran, and civilian culture. Service members and veterans should be involved in every step of the design, testing, and roll-out of orthoses, assistive devices, and other supportive technologies. Examples of participatory design are shown in Figure 4.2. Technology enables greater inclusion and changes activity and participation for limb-salvage patients and others with limited mobility. These changes can range from web-enabled applications that monitor activity to exoskeletons and robotic arms that operate kitchen appliances. Additional research on the next generation of tools should include alternative and longer-lasting power sources and encouraging private-sector participation and partnerships.

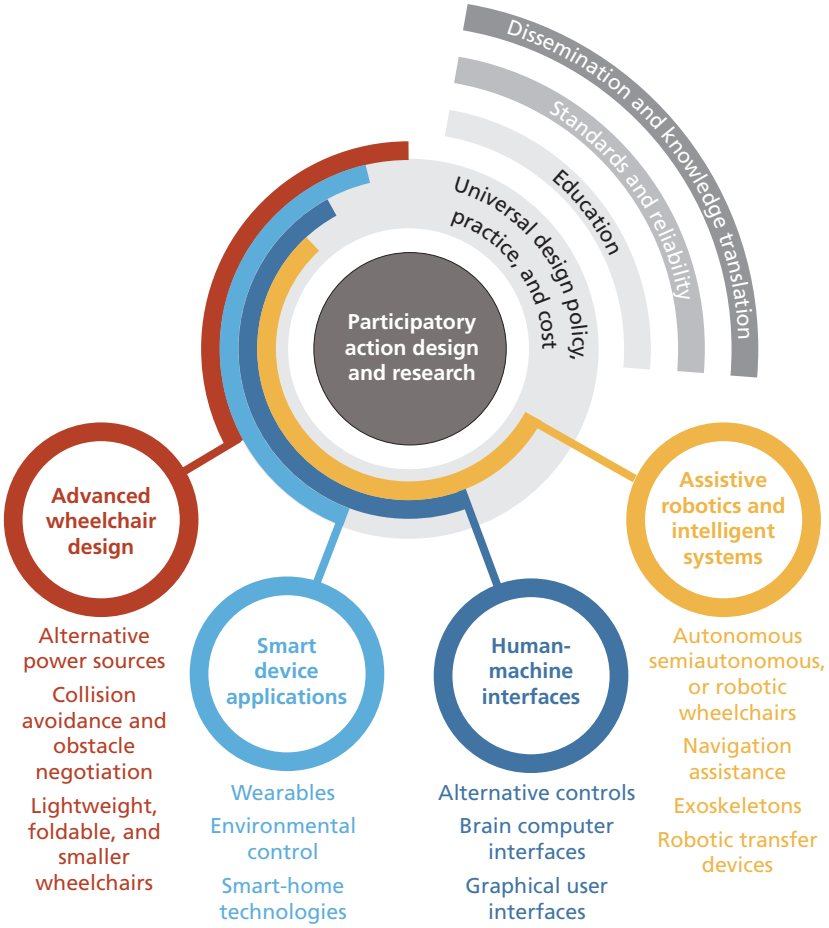
Hypertrophic and Contracted Scars Are Burn Patients' Most Valuable Reconstructive Anatomy

Dr. Matthias Donelan, M.D. (Shriners Hospitals for Children), presented the current clinical practice for scars. The field has changed dramatically over the past 30 years. Donelan argued the following: "Elimination of scars is a chimera. Accepting them is achievable." After a century of excising scars and scarred tissue, scars are now rehabilitated with medical lasers and simple plastic surgery techniques. Burn and trauma patients' own hypertrophic and contracted scar tissue can be their most valuable asset. In addition to better visual appearance, this method allows skin to regenerate, minimizes complications, and requires no iatrogenic donor sites. For blast patients with thermal injury, clinicians should focus on long-term outcomes that enhance mobility and decrease scarring.

Rehabilitation of the Blast Casualty: Lessons Learned from Past and Current Conflicts

COL (Ret.) Paul Pasquina, M.D. (Walter Reed National Military Medical Center), shared an overview of rehabilitation practices for amputee and limb-salvage patients and the lack of knowledge on long-term outcomes. He contended that surgeons need to take a greater role in rehabilitation to both mitigate complications and risks and lessen postoperative time in the

Figure 4.2
Examples of Participatory Design



SOURCE: Rory Cooper, eighth SoSM.

intensive care unit. To achieve these goals, Pasquina recommended the following: (1) maintaining interdisciplinary centers of excellence, (2) incorporating behavioral health and rehabilitation principles early, (3) limiting convalescent leave, (4) implementing comprehensive pain management, (5) implementing peer-support programs that include fellow soldiers and family, (6) VA-DoD partnerships, (7) integrative medicine, and (8) increased public awareness about people with disabilities.

In addition, Pasquina noted that there have been no long-term studies of aging with limb salvage. Prospective studies need to be planned on biomechanical effects, physiologic changes, and the impact on activities for service members with limb injuries transitioning to the VA. The METALS cohort study (discussed in Chapter Two) found that one-third of enrollees in the study were on active duty, in school, or not working, and nearly 40 percent were depressed. Patients with amputations had more-aggressive rehabilitation and lower likelihood of PTSD than patients with limb salvage.

CHAPTER FIVE

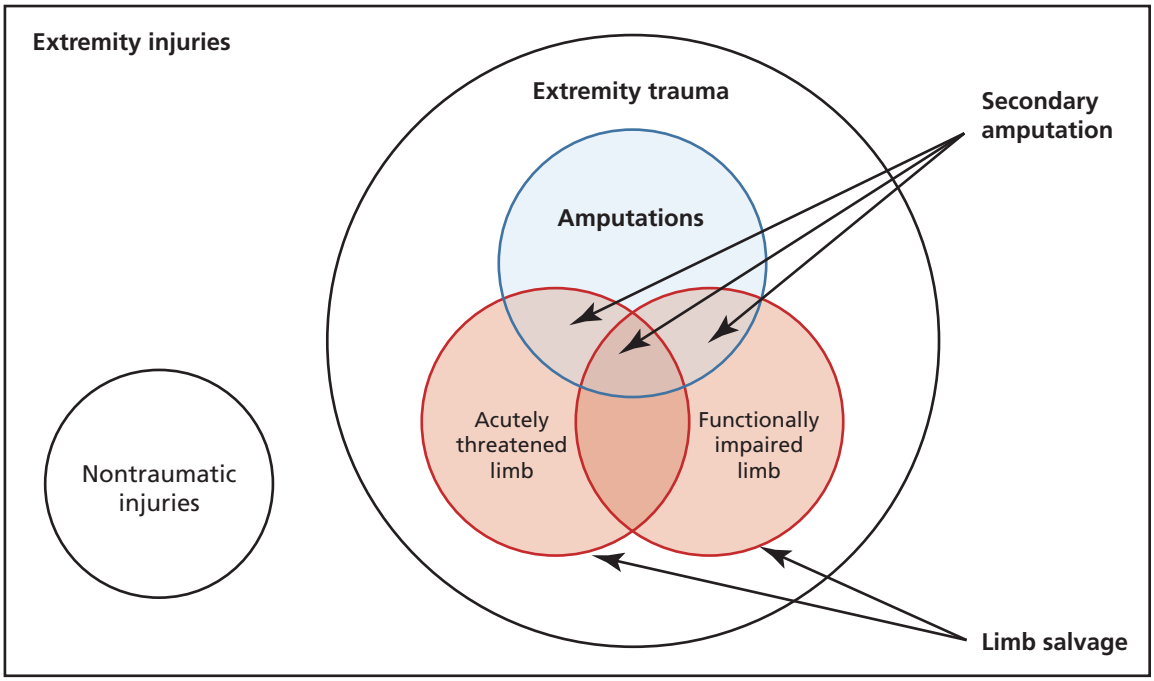
Scientific Presentation Summaries

This chapter provides summaries of the scientific presentations from notes taken by the RAND team during the SoSM. In consultation with the planning committee, the RAND team selected abstracts to accept for oral presentations upon evaluation of the title and the abstract.

Identification of a Combat-Related Limb Salvage Cohort

Dr. Steven Goldman, Ph.D. (DoD/VA Extremity Trauma and Amputation Center of Excellence), spoke on the difficulty of identifying limb-salvage patients because of inconsistent definitions. Illustrated in Figure 5.1, lower-extremity injuries include bony-tissue and

Figure 5.1
Lower-Extremity Injuries



SOURCE: Steven Goldman, eighth SoSM.

soft-tissue loss and limb retention without the need for amputation, and they require operative treatment.

To study the limb-salvage population, Goldman and his colleagues selected a cohort of patients who had at least one lower-extremity traumatic injury and identified a surrogate population of those who underwent amputation 15 days or more post-injury. The team reviewed all initial encounter International Classification of Diseases (ICD), Ninth Revision (ICD-9) codes associated with the injuries, determined the relative frequency of these codes, extrapolated to the entire combat injury population, and validated the approach with subject-matter experts (SMEs). Overlap with polytrauma codes was common, but the data-driven approach pulled out rehabilitation codes that the SMEs overlooked. However, the approach failed to capture nerve-related operations, such as nerve grafting, that were identified by SMEs. The group will use the same approach to study upper-extremity injuries and expand it to use ICD-10 codes to increase future utility.

Outcomes After Heel Pad–Degloving Injuries

Dr. Michael Bosse, M.D. (Major Extremity Trauma Research Consortium), suggested that the heel pad is an overworked and underappreciated anatomic structure and that reconstruction after severe injury is limited by insufficient tissue for primary closure. Without adequate tissue, a patient needs a skin graft over the foot to allow for normal walking. Bosse hypothesized that patients who require flap coverage would have experienced better outcomes had they undergone early amputation. Retrospective analysis of several studies compared functional outcomes of patients who underwent primary or secondary closure, flap coverage, or amputation. Findings supported the hypothesis and confirmed that, regardless of soft tissue closure, patients had significant disability following a severe ankle or hindfoot injury associated with heel pad degloving.

Tissue Engineering for Limb Salvage: A Prospective, Randomized Controlled Trial of Dehydrated Human Amnion/Chorion Membrane

Dr. Frank Lau, M.D. (Louisiana State University), lectured on many of the shortcomings of flap-based limb salvage (fLS). fLS is often bulky and deforming, requires revisions, is expensive, and requires a microsurgeon. Often, mistakes made along the way lead to amputation. In future multidomain operations environments, evacuation time might be delayed, and patients likely will not have access to a microsurgeon, making fLS an approach that is unlikely to be used. As an alternative, Lau and his colleagues proposed tissue engineering limb salvage (teLS) using a dehydrated human amnion/chorion membrane (dHACM) to engineer stable soft tissue over bones and tendons. A definitive closure can be achieved with split-thickness skin grafting. Lau described a 53-person randomized controlled trial with crossover to find primary reconstruction success with teLS. Patients in the treatment arm of the trial had a shorter operative time and fewer procedures and incurred lower costs than those in the control arm. dHACM treatments can be performed in outpatient settings, extending their feasibility to lower-resourced or mass-casualty situations.

Beyond Limb Salvage: Minimizing Pain and Maximizing Function Through an Orthoplastic Approach to Limb Restoration in Combat-Injured Extremities

LTC(P) Benjamin Potter, M.D. (Walter Reed National Military Medical Center), spoke on the components and challenges of moving beyond the limb-salvage paradigm since the OIF and OEF conflicts began. Limb salvage tends to align with the combat casualty load (see Figure 5.2, which shows the number of limb-salvage procedures and limb-restoration procedures from 2011 to 2018). The changing operational tempo, particularly since 2015, means that limb-salvage procedures have rapidly decreased without the opportunity for reflection on, or crystallization of, lessons learned from the period of increased combat casualty.

Potter also offered a multistep process for limb salvage, starting at point-of-injury care and moving to limb preservation, limb salvage, and eventually limb restoration, as illustrated in the field care timeline in Figure 5.3.

Limb-restoration efforts aim to minimize pain and maximize function. They can be divided into four categories: pain via targeted muscle reinnervation, function via osseointegration, sensation via nerve transfers or sensate flaps, or durability via flap resurfacing or soft tissue contouring. As surgical techniques improve, the paradigm is evolving from limb salvage to limb restoration, in which the effort is made not only to save the limb but to return it to its earlier function. These two surgical techniques—limb salvage and limb restoration—have created a feedback loop in which each shares lessons learned and challenges. In addition to presenting surgical challenges, limb restoration places an increased demand on care coordination across different systems and locations of care and integration with competing priorities. Patients are spread out geographically and require years of follow-up support. Furthermore, as the nature of injuries changes and experts retire from military service, support needs to be sustained at the professional level to maintain levels of medical expertise.

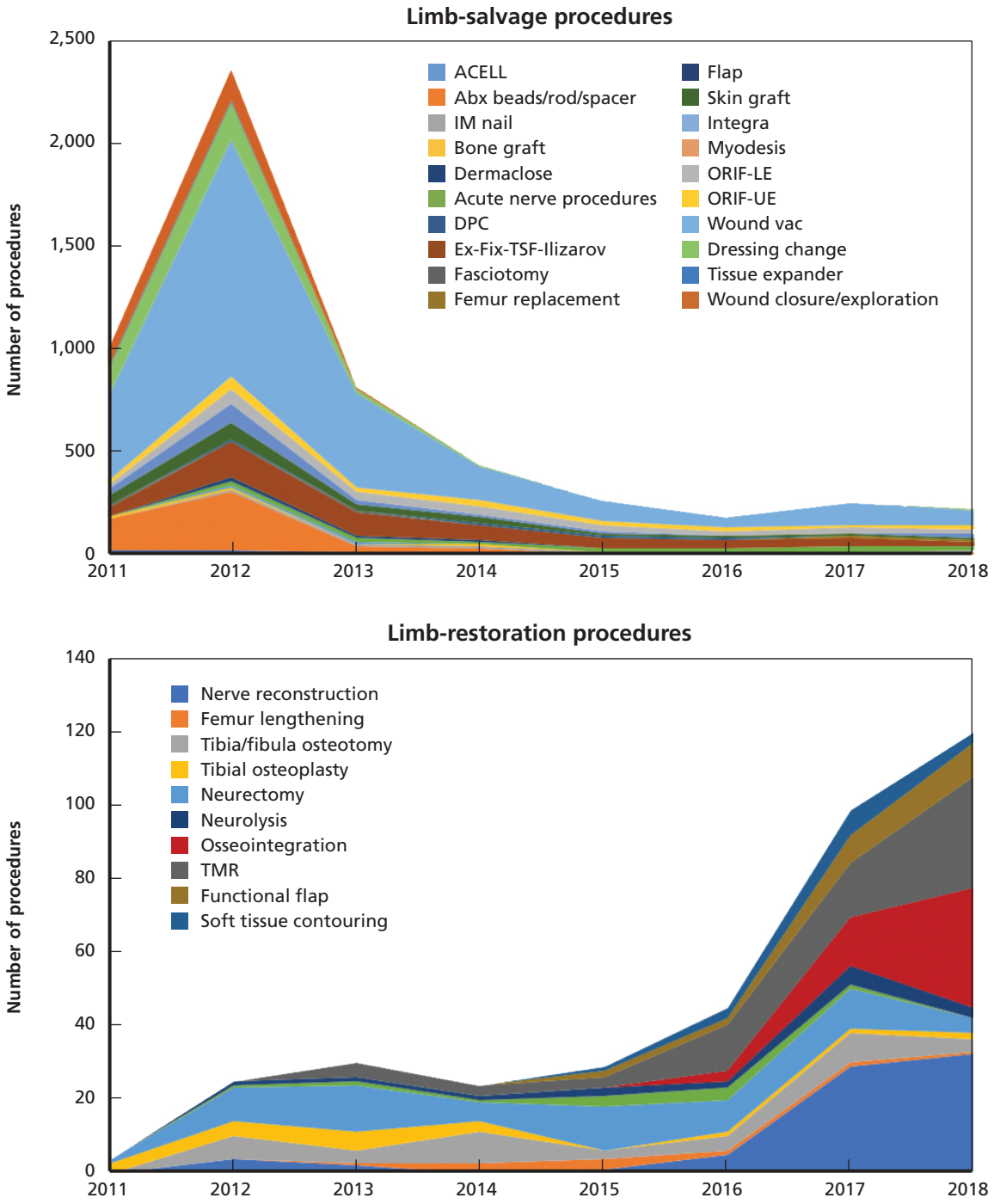
Acellular Fish Skin Graft

CDR (Ret.) Marvin Blake McBride III (Kerecis), shared Kerecis's recent advances using discarded fish skin for human skin regeneration. Fish skin and human skin share common structural components, including collagens, elastin, laminin, fibronectin, glycans, proteoglycans, and lipids. Kerecis is investigating ways in which this technology can improve, and increase the speed of, wound healing. To date, fish skin patches have been FDA approved for chronic wounds, such as diabetic ulcers, pressure ulcers, surgical wounds, and draining wounds, as well as traumatic wounds, such as abrasions, second-degree burns, or skin tears. Applications for third-degree burns, oral surgery, and hernias are in development. Fish skin patches are stable at room temperature for at least three years, and, in larger sheets, they might serve as a cover for open wounds and can be combined with topical antibiotics. A larger trial at MedStar Washington Hospital Center for full-thickness burns will start recruiting patients soon.

Polyethylene Glycol Fusion Improves Recovery of Peripheral Nerve Injuries

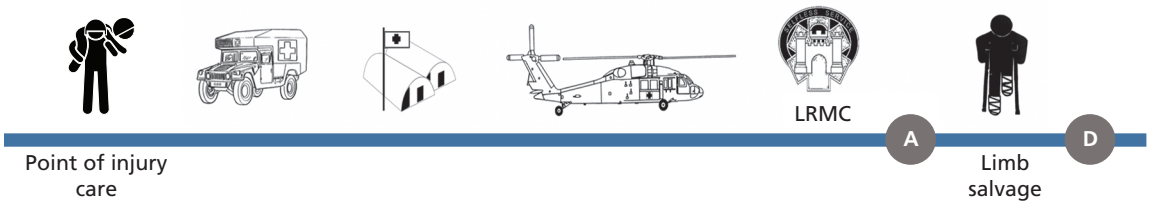
Dr. Jaimie Shores, M.D. (Johns Hopkins University), spoke about the difficulty of preserving nerve function after the axons have been severed. The scope of peripheral nerve injuries

Figure 5.2
Changing Practice Patterns, 2011–2018



SOURCE: Adapted from Harrington et al., 2020. Used with permission.
NOTES: DPC = direct primary care. IM = intramedullary. ORIF-LE = open-reduction internal fixation—lower extremity. ORIF-UE = open reduction internal fixation—upper extremity. TMR = transmyocardial laser revascularization. TSF = Taylor Spatial Frame.

Figure 5.3
A Limb Preservation Timeline



SOURCE: Benjamin Potter, eighth SoSM.
NOTE: LRMC = Landstuhl Regional Medical Center.

(PNIs) is poorly characterized, and treatment algorithms are based on expert opinion instead of quantitative analyses. To estimate PNI incidence, Shores used a retrospective review of insurance data to extrapolate 67,800 major PNIs in the United States annually. In terms of lost wages, nerve injuries were the costliest. For upper-extremity injuries in civilians, 59 percent of patients with median or ulnar nerve injuries were likely to return to work within a year, while patients with injuries to both nerves had only a 24-percent chance of returning to work at any point in time. In a military context, PNIs account for over 50 percent of all combat-related disabilities. The METRC nerve study prospectively followed upper-extremity major PNI, looking at global and patient-reported motor and sensory outcomes. Shores and his team tracked each type of nerve repair and found the ratio of allografts to autografts to be nearly 3:1. Polyethylene glycol (PEG)–mediated axonal membrane fusion, or PEG fusion, aims to bypass genetically programmed disability from Wallerian degeneration. The process for PEG fusion is illustrated in Figure 5.4.

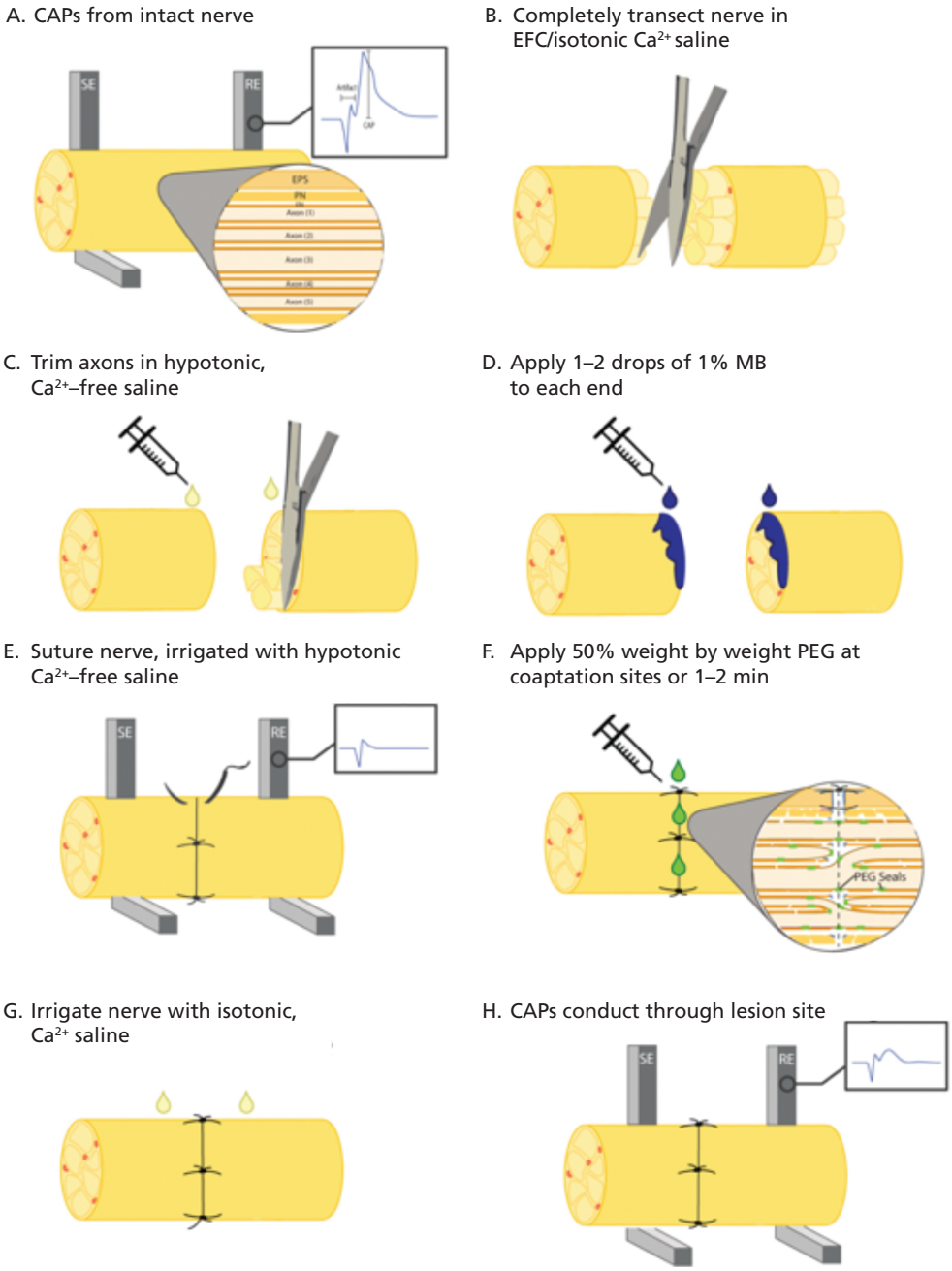
Studies in rats found that more axons were fusing than those left to heal on their own when PEG fusion was used. If human trials are successful, PEG fusion in mixed nerves could change the treatment algorithm for nerve repair and reconstruction and provide some immediate functional improvements. However, use of PEG fusion would also require surgery to be performed within 48 hours of injury, instead of after days to weeks of waiting for nerve repair.

Using Regenerative Medicine to Repair Wounded Limbs

COL David Saunders, M.C. (U.S. Army Medical Materiel Development Activity [USAMMDA]), shared USAMMDA's role in translating research into clinical and fielded developments. Integrating the DoD acquisitions and regulatory processes, USAMMDA serves as an industrial partner to bring products to scale and bring stakeholders together (Figure 5.5).

As DoD prepares for future conflicts, USAMMDA is preparing for several areas of regenerative medicine: burn treatment, with a focus on pre-burn treatment center care; extremity repair, consisting of vascular injuries, volumetric muscle loss, peripheral nerve repair, and bone and connective tissue; noise-induced hearing loss; and regenerative medicine manufacturing. Despite a 90 percent post-injury survivability rate in recent conflicts, the United States is unprepared for a large-scale conflict requiring prolonged field care. Strengthening regenerative medicine at the point of care could promote earlier healing and return to function. Reconstructive surgeons need a regenerative medicine "tool kit" that addresses vascular, bone, connective tissue, nerve, and muscle needs. An optimal tool kit is shown in Table 5.1.

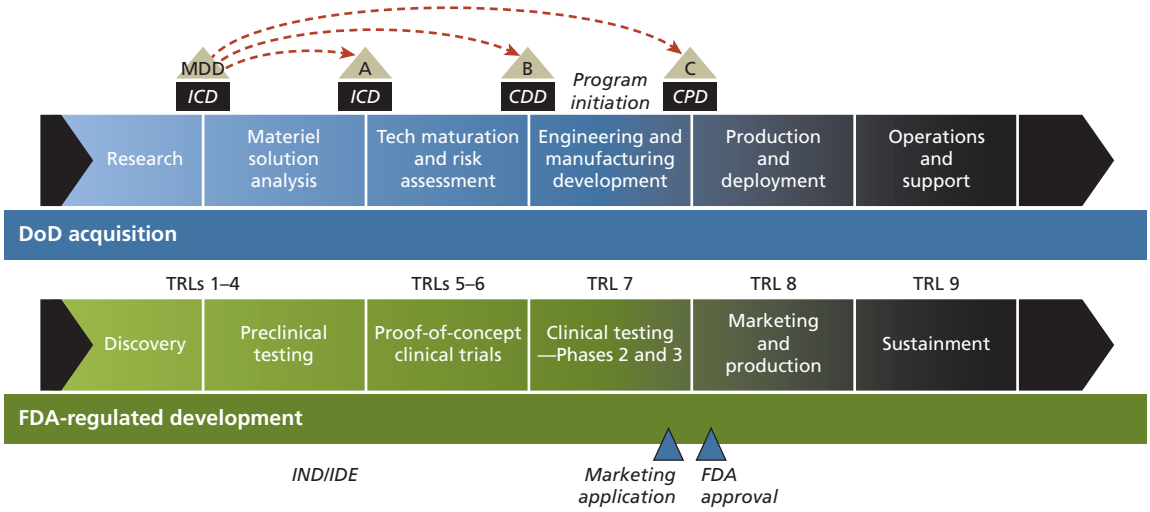
Figure 5.4
Polyethylene Glycol Fusion



SOURCE: Ghergherehchi et al., 2019, p. 4. Used with permission.
NOTES: Ca^{2+} = calcium ion. CAP = compound action potentials. ECF = extracellular fluid. MB = methylene blue.

To provide structural integrity, successful approaches are likely to incorporate combinations of autologous and/or allogeneic stem cells, growth factors, decellularized tissue conduits, and engineered biomaterials. A target product profile is shown in Table 5.2. It can be used as a guide point for FDA approval of potential candidate drugs or devices. Any candidate needs

Figure 5.5
Translating Research into Products



SOURCE: David Saunders, eighth SoSM.
NOTES: CDD = Capabilities Development Document. CPD = Capabilities Production Document. ICD = Initial Capabilities Document. IND/IDE = investigational new drug/investigational device exemption. MDD = medical device development. TRL = technology readiness level.

to be versatile, working in multiple types of tissues or situations. The ideal is a product that supports composite tissue.

A Single-Shot Diagnostic for Nerve Injury in Mangled Limbs

Dr. John Elfar, M.D. (Pennsylvania State University), argued that, when addressing limb salvage, all clinicians are rehabilitation doctors. The golden question in severe limb trauma is, "Is the nerve severed or crushed?" Nevertheless, in most trauma cases, the care team does not know whether the nerve was severed. Severe limb trauma affects different types of tissue, and each type has its own diagnostic test that helps determine the appropriate clinical intervention. However, peripheral nerves do not have a test to diagnose the presence or quality of function. Peripheral nerves cannot be tested for six weeks after the injury, delaying decisions on whether to perform surgery and subsequent rehabilitation. Elfar and his colleagues used large doses of 4AP to identify and diagnose lesions with axonal continuity. Instead of examining nerves surgically, the team used 4AP to block potassium leakage from demyelinated axons (Figure 5.6).

Elfar found that "the crush-injured nerve, though functionally indistinguishable from the completely severed nerve, can be demonstrated to have intact fibers capable of supporting function." 4AP was immediately diagnostic of incomplete injury. Elfar's team has submitted an investigational new drug application for a single-dose systemic trial in traumatically paralyzed limbs.

Table 5.1
The Army's Extremity Repair Effort

Tissue (Technology Readiness Levels)	Receiver Operating Characteristic	Target Improvements	Current Treatment Options	Limitations
Vascular (7)	2–4	Sizable engineered tissue graft with long-term patency and reduced infection rates	Autograft	Finite resource
			Synthetic graft	Poor long-term viability
			Synthetic stent graph	Small repairs only
Nerve (4)	4	1. Short term—improved nerve regrowth rates 2. Medium term—maintain NMJ; electrical stimulation 3. Long term—prevent Wallerian degeneration	Autograft	Finite resource; poor outcome
			Allograft/cadaveric	Immunosuppression
			Synthetic conduit	Poor outcomes > 3 cm
Bone (4)	2–4	1. Forward stabilization—resorbable "fracture putty" 2. Non-union—non-immunogenic allograft 3. Prevent posttraumatic OA	Bone grafting	Infection, resorption
			Bone transportation/ external fixation	Infection risk
			"Fracture putty"	Non-load-bearing
Muscle (4)	4	1. Prevent and treat VML 2. Composite tissue regeneration 3. Musculotendinous junction	Flap construction	High failure rates (up to 30 percent), poor outcome
			Tendon transfers	

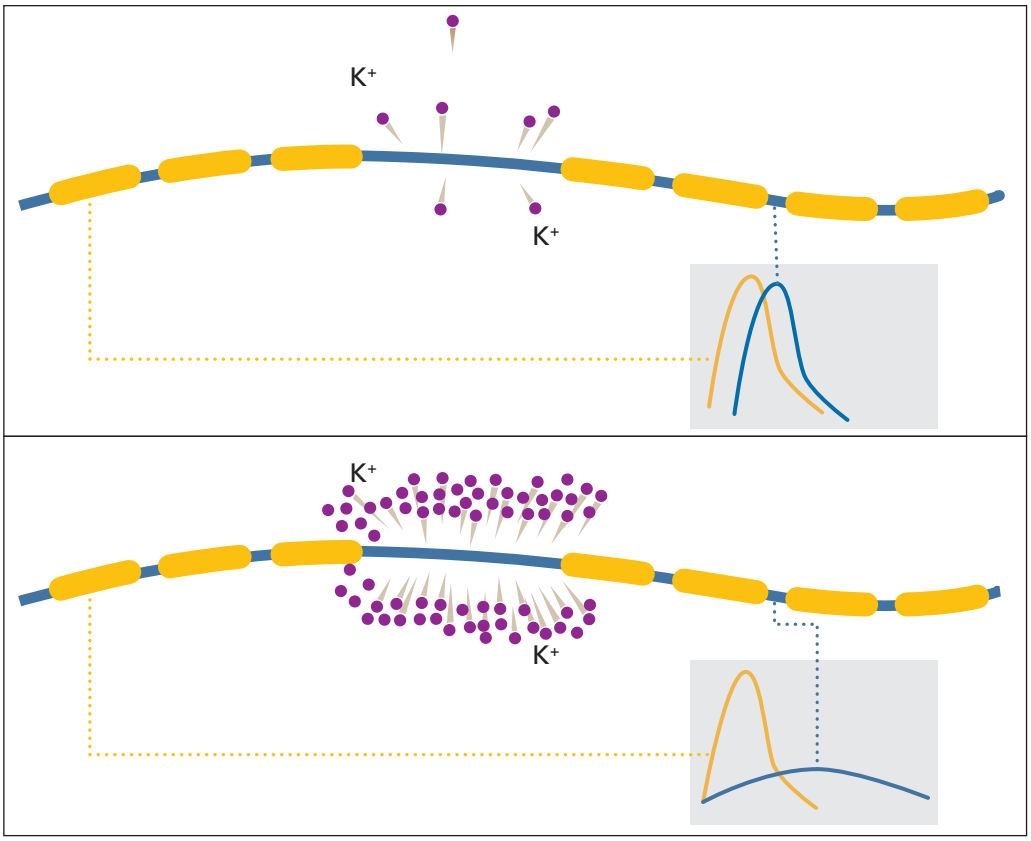
SOURCE: David Saunders, eighth SoSM.
NOTES: NMJ = neuromuscular junction. OA = osteoarthritis. ROC = receiver operating characteristic. TRL = technology readiness levels. VML = volumetric muscle loss.

Table 5.2
Target Product Profile for Extremity Trauma

Parameter	Threshold	Objective
FDA approval/clearance	Confirmation of efficacy in humans	Trauma indication
Maximally restorative	≥ 50-percent improvement in form and function over standard of care	Restores native tissue form and function
Reduces need for autograft	Reduces need for autograft	Eliminates need for autograft
Efficient	≤ 50-percent reduction in number of surgeries and/or recovery time	> 50-percent reduction in number of surgeries and/or recovery time
Safety	≤ 50-percent reduction in rates of infection and/or complication	> 50-percent reduction in rates of infection and/or complication
Well tolerated	Reduces pain and/or comorbidities associated with care over standard of care	Eliminates associated pain and/or comorbidities
User acceptance	Selected by potential users over current standard of care options	T = O

SOURCE: David Saunders, eighth SoSM.
NOTE: T = O means acceptance of new care over current standard.

Figure 5.6
The Effect of 4-Aminopyridine on Damaged Nerves



SOURCE: John Elfar, eighth SoSM.

Immune-Directed Therapy to Prevent Heterotopic Ossification and Extremity Injury

Dr. Benjamin Levi, M.D. (University of Michigan), offered an overview of heterotopic ossification (HET OSS or HO) resulting from traumatic injury. Up to 50 percent of cases will develop HET OSS, including a growing number of nontraumatic cases, such as hip replacements. Current HET OSS strategies are inadequate because of limited knowledge of risk factors and a lack of standards for early diagnostic strategies, proven treatments, treatment timing, occupational therapy protocols, and the role of nerve innervation. The Boston-Harvard Burn Injury Model System developed a HET OSS risk calculator, but it only indicates whether the HET OSS will form, not where. Bone morphogenetic protein (BMP) inhibition prevents HET OSS. Levi's team used single-cell RNA sequencing (scRNAseq) to identify the cellular composition at the injury site. They found five categories of mesenchymal cells causing this process. BMP causes inflammation and HET OSS, so treatments must be targeted and strategic. In murine (rodent) studies, mobilizing subjects for one week after injury eliminated inflammation and prevented HET OSS formation. For humans, current thinking avoids immobilization to preserve range of motion. However, movement after injury augments inflammation by disrupting local tissue microstructure; thus, a paradigm shift for surgeons

and rehabilitation experts might be in order. In addition, Levi and colleagues found that neutrophil extracellular traps form where HET OSS forms along the fascial plane, and these could serve as a biomarker.

Nanoemulsion Against Drug-Resistant Wound Infections

Dr. Suhe Wang, M.D., Ph.D. (University of Michigan), presented on wound infections, one of the leading causes of combat-related morbidity and mortality. A new generation of safe, broadly effective, and easily applied antimicrobials is needed to prevent infection of blast injuries without interfering with wound healing. Wang's team developed a broadly active topical nanoemulsion-based therapy to prevent infection and treat traumatic wound infections. The particles are small enough that they can pass through pores and hair follicles without entering the intercellular junctions surrounding epithelial cells, thereby allowing nanoemulsion to deeply penetrate skin tissues. The particles then concentrate at the site of an infection and surround infectious organisms, where the particles are driven to fuse with the outer membrane of the pathogen. In testing the therapy in pigs with abrasions and partial thickness burns infected by Methicillin-resistant *Staphylococcus aureus* (MRSA), the team found benefit in treating both models.

Nerve Crush Injury Treatment: 4-Aminopyridine

Dr. M. A. Hassan Talukder, M.B.B.S., Ph.D. (Pennsylvania State University), argued that there is an unmet need for new therapeutic strategies to promote functional recovery, reduce long-term disability, and improve the quality of life in patients with traumatic peripheral nerve injury (TPNI). TPNI is highly prevalent in blast injuries, though treatment is frequently delayed in favor of emergent resuscitation and damage control and in preparation for later surgical repair. This not only delays recovery but also misses the window of opportunity for reinnervation and functional recovery. Talukder hypothesized that 4AP could protect denervated muscle by remyelination and improved conduction velocity of the nerve in skeletal muscle. Through testing in mice, he found that 4AP improves *in vivo* global motor function following sciatic nerve crush injury and reduces muscle atrophy in the injured limb. Because 4AP has already been FDA approved for multiple sclerosis patients, several formulations are available for future studies of this potential neuromodulatory agent.

CHAPTER SIX

Accepted Poster Abstracts

This chapter provides abstracts of the poster presentations, as submitted by the author(s) to this SoSM. In consultation with the expert panel, the RAND team selected abstracts to accept for poster presentations upon evaluation of the title and the abstract.

Poster Presentation by Dr. Vlado Antonic

Walter Reed Army Institute of Research [WRAIR], Wound Infection Department

Blast Effects on Infection and Antibiotic Disposition

Dr. Vlado Antonic,[1] LTC Chad Black,[2] MAJ Samandra Demons,[3] Dr. Joseph Long,[4] LTC Stuart Tyner[5]

Objective

The combined effects of blast and shrapnel contribute to a high incidence of multiple complex wounds to the extremities characterized by extensive soft tissue and bone destruction in our troops. Rapid and effective wound healing is a major treatment goal for the military medical community. Wound infections are key contributing factors to the life-altering sequela of wounds, such as deformity and amputation of extremities. There are limited data on the effects of blast overpressure (BOP) on infection development and therapeutic efficacy of antibiotics. Here, we present Walter Reed Army Institute of Research's efforts to address this knowledge gap in the pathophysiology of blast-related wound infections by combining the institutes' unique blast, infection, and pharmacology research capabilities: (1) host response to combined blast and soft tissue injury; (2) BOP effects on infection development; and (3) BOP effects on antibiotic pharmacokinetics and dynamics. We performed a series of three experiments to gain a better understanding of these effects.

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[1] Wound Infections Department, Walter Reed Army Institute of Research.

[2] Experimental Therapeutics Branch, Walter Reed Army Institute of Research.

[3] Wound Infections Department, Walter Reed Army Institute of Research.

[4] Blast Induced Neurotrauma Branch, Center for Military Psychiatry and Neurosciences, Walter Reed Army Institute of Research.

[5] Wound Infections Department, Walter Reed Army Institute of Research.

Material/Methods

All experiments are performed in male BALB/c mice. Cyclophosphamide (CP, immunosuppressing agent) pre-treatment at days –4 and –1 was given to positive controls. All the animals were exposed to 19psi BOP using high-fidelity blast simulator at WRAIR.

Experiment 1. Blast- and CP-treated animals (n = 160) were euthanized on days 1, 2, 3, 4, 5, 6, 7, and 14, blood was collected using [ethylenediaminetetraacetic acid] EDTA tubes, and blood cell numbers were determined using HemaVet 950FS.

Experiment 2. The animals (n = 60) were subdivided to receive CP, blast, or Sham. Each group was subdivided to receive incisional wound or infected incisional wound. Infection was established using bioluminescent A. banumanii 5075 in a dose of 5x10^4 CFU (colony-forming units)/wound. Animals were followed for 15 days. At days 1, 3, 5, 7, 9, 11, 13 and 15, we collected photographs of the wounds and determined rates of wound healing. On same days, we determined bacterial burden in situ using IVIS *in vivo* imaging system.

Experiment 3. A total of 160 animals were divided to Sham and blast. At 1h after the exposure, all the animals received an i.v. injection of cefazolin. Animals were euthanized at 3 min, 10 min, 15 min, 30 min, 1h, 3h, 6h or 10h after the injection. Plasma and liver were analyzed for concentration of cefazolin using mass-spectrometry.

Results

Experiment 1. We observed significant decreases in the number of immune cells in the blood of animals exposed to blast when compared to sham controls. The effects of blast were comparable to the CP treatment.

Experiment 2. We observed trend increases in the number of bacteria in wounds of blast-exposed animals when compared to Sham at early time points. Blast exposure did not result in a delay in wound healing.

Experiment 3. We observed increases in the concentration of cefazolin in the plasma and liver of blast-exposed animals at later time points and increases in the elimination of half-life.

Conclusion

Our results suggest that blast induces a wide spectrum of immunological, physiological, and pharmacokinetic effects that may cumulatively promote infection development and hamper antibiotic therapeutic efficacy for combat wounds.

Disclaimer

Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation/publication.

Poster Presentation by Dr. Alan R. Davis

Baylor College of Medicine, Center for Cell and Gene Therapy

The Blood-Nerve Barrier and Heterotopic Ossification

Dr. Alan R. Davis,[6] Dr. Elizabeth A. Davis[7]

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[6] Baylor College of Medicine.

[7] Baylor College of Medicine.

Blast injury is the major cause of heterotopic ossification (HO) in the military (1). There are two types of HO—new bone fused to skeletal bone and an island of new bone in the muscle. The second type is called neurologic HO (2). We have found that neurologic HO is basically a breakdown of the blood-nerve-barrier that allows [bone morphogenetic protein 2] BMP2 to enter the nerve and also enables the migration of chondro-osseous cells and other "support" cells out of the nerve and into the muscle (3–6). If the BNB [blood-nerve barrier] is intact, BMP2, which is the ultimate cause of HO in humans (4), cannot enter the nerve, nor can chondro-osseous and other cells leave the nerve (7). This is true in rats and humans, but not in mice. The reason for this is anatomical: Mice have only a single fascicle per nerve and a thinner perineurium than rats or humans and an almost nonexistent epineurium. Therefore, injection of BMP2-producing cells into mice, but not rats, causes neurogenic HO (7). Only if the rat nerve is injured does injection of BMP2-producing cells into muscle produce HO. In the mouse, with its BNB "partially" open, we have recently collected data that suggest, using the technique of single-cell RNA seq (8), that neurogenic HO begins with neural stem cells in peripheral nerves. These data support the notion that the first chondro-osseous cell to appear expresses transcripts of both the chondrocyte and osteoblast lineages and that this chondro-osseous progenitor (COP) gives rise to one osteoblast (O) and four chondrocyte (C1 to C4) cell types, with the COP giving rise to both O and C1. Then C1 gives rise to C2 and C2 to C3 and C4. Analysis of the transcriptomes of these chondrocyte cell types indicates that C1 and C2 are early chondrocytes, while C3 and C4 are or are becoming hypertrophic chondrocytes.

1. Potter BK et al. Heterotopic ossification following combat-related trauma. *J. Bone Joint Surg. Am*. 2010 Dec;92 Suppl 2:74–89.
2. Davis EL et al. Is heterotopic ossification getting nervous?: The role of the peripheral nervous system in heterotopic ossification. *Bone.* 2018;109:22–7.
3. Lazard ZW et al. Osteoblasts have a neural origin in heterotopic ossification. *Clin. Orthop. Relat. Res.* 2015 Sep;473(9):2790–806.
4. Olmsted-Davis EA et al. Progenitors in peripheral nerves launch heterotopic ossification. *Stem Cells Transl. Med.* 2017. Apr;6(4):1109–19.
5. Gugala Z et al. Trauma-Induced Heterotopic Ossification Regulates the Blood-Nerve Barrier. *Front. Neurol.* 2018 Jun 5;9:408.
6. Palladino SP et al. The Human Blood-Nerve Barrier Transcriptome. *Sci. Rep.* 2017 Dec 12;7(1):17477.
7. Davis EL et al. Location-dependent heterotopic ossification in the rat model: The role of activated matrix metalloproteinase, *J. Orthop. Res.* 2016 Mar 14;34(11):1894–904.
8. Zheng GXY, et al. Massively parallel digital transcriptional profiling of single cells. *Nat. Commun.* 2017 Jan 16;8:14049.

Poster Presentation by Dr. Neal M. Lonky

University of California, Los Angeles; MediTech Development, Inc.

Vacuum Tourniquet for Tamponade of Penetrating Injuries

Dr. Neal M. Lonky[8]

Penetrating injuries with vascular injury to areas of the body not amenable to conventional long-term tourniquet tamponade would require manpower to apply care and pressure to the wound site. Significant bleeding would involve large doses of therapeutic clotting drugs at high cost. The technology demonstrated in the abstract presented will describe the pairing of an automated and compact vacuum pump system paired with a proprietary vacuum cup device that could be tailored for different areas of the body. This includes upper limbs, torso, abdomen, thorax, and internal organ lacerations if exposed. This presentation will showcase the pump-and-cup technology specifications, demonstrate capability of the pump as a proof of function, and provide a simulation of a laceration wound using the new technology, compared with standard vacuum cups in practice today. The benefit of patent-protected adjunct use of the technology to deliver drugs in concert with tamponade will be discussed.

Disclaimer

Dr. Lonky is co-founder of MediTech, shareholder and officer, and inventor of technologies discussed.

Poster Presentation by CDR Blake McBride

Kerecis, LLC

Omega3-Rich Fish Skin as an Infection-Prevention Strategy

CDR Blake McBride,[9] Skuli Magnusson,[10] Dr. Baldur Tumi Baldursson,[11] Dr. Hilmar Kjartansson,[12] Gudmundur Fertram Sigurjonsson[13]

Introduction

Use of improvised explosive devices (IEDs) in modern warfare has increased the frequency of blast injuries. Victims of explosions often suffer from multiple traumatic injuries with a high risk of wound infection. The most frequently multidrug-resistant identified drug resistant strains of bacteria are *Staphylococcus aureus*. Current pre-hospital treatments for blast-related injury involve simple nonbioactive dressings to limit secondary wound contamination. No viral or prion disease transmission risk exists between Atlantic cod and humans, thus allowing for gentle processing and therefore preservation of the natural elements of the fish skin. Mammalian-derived tissues, however, require treatment with harsh detergents because of disease transmission. Randomized and double-blind clinical trials have shown that cod fish skin promotes faster healing in acute wounds compared to a mammalian-derived product. Fish skin

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8 MediTech Development Corporation.

9 Kerecis LLC.

10 Kerecis LLC.

11 Kerecis LLC.

12 Kerecis LLC.

13 Kerecis LLC.

is adapted to the constant threat of invading pathogens in the aquatic environment. Kerecis™ Omega3 is FDA-cleared acellular fish skin that has multiple natural biomechanical properties that facilitate tissue protection and regeneration.

Objective

The objective of this study was to assess the ability of cod fish skin to act as a barrier to bacterial invasion.

Method

Biomaterials (1.5 cm x 1.5 cm) were placed between a two chamber apparatus. Broth with log 4.0 CFU/ml of *Staphylococcus aureus* (ATCC [American Type Culture Collection] 25923) was injected into the upper chamber and sterile broth into the lower chamber. Kept at 37°C until breached by S. aureus, calculated from S. aureus growth curve.

Results

The fish skin is a more effective barrier to S. aureus compared to Puraply™ (Organogenesis) type I porcine collagen matrix, Epifix® (Mimedx) human amniotic membrane allograft, and Endoform (Hollister) dermal template dressing. Spiking the Omega3 content of the fish skin further augments its barrier properties.

Conclusion

The Kerecis Omega3 fish skin technology is an effective bacterial barrier compared to mammalian tissues. The bacterial barrier and hemostatic properties confirmed in additional research, combined with the storage and shelf-life properties, indicate that Kerecis Omega3 offers an innovative and efficient solution for advanced treatment options for the DoD related to blast-related injuries.

1. Calhoun, J. H., Murray, C. K. & Manring, M. M. Multidrug-resistant Organisms in Military Wounds from Iraq and Afghanistan. *Clin. Orthop.* 466, 1356–1362 (2008).
2. Desbois, A. P. & Lawlor, K. C. Antibacterial Activity of Long-Chain Polyunsaturated Fatty Acids against Propionibacterium acnes and Staphylococcus aureus. *Mar. Drugs* 11, 4544–4557 (2013).
3. Magnusson, S. et al. Decellularized fish skin: characteristics that support tissue repair. *Laeknabladid* 101, 567–573 (2015).

Disclaimer

The authors and presenter are full or partial employees of Kerecis LLC.

Poster Presentation by Justin McKee

U.S. Army Research Laboratory

Characterizing Blast Environment for Extremity Protection

Justin McKee,[14] Robert Spink,[15] Dr. David Fox[16]

Improvised explosive devices (IEDs) have been used widely in recent conflicts. These threats propel soil at high velocities, causing extensive soft tissue damage to the extremities with poor treatment prognosis, long-term physiological and psychological complications that reduce quality of life, and high health care costs. The extremities are particularly susceptible to injury from explosively propelled soil because they have less protection compared to the torso. Although it is desirable to add protection to reduce injury, designing protection for the extremities is a challenge because of the need to keep the weight low and maintain flexibility and comfort where joints such as the knee and hip require a large range of motion. Our approach is to develop experimental and modeling techniques that will enable us to evaluate and optimize the protective qualities of fabric used to make combat uniforms. First, we conducted full-scale arena experiments to characterize the blast environment where extremity injuries are likely to occur. Specially designed experimental fixtures allowed us to image a section of the soil spray with high-speed video and models of the explosion assist with characterizing the blast environment by providing data that cannot be captured with cameras and sensors. Next, we developed a yarn-level finite element model of the Army Combat Uniform subject to soil blast loading to better understand stress propagation in the fabric and mechanisms of failure. Design characteristics of the uniform, such as fiber material and weave patterns, can be modified in the model in an effort to improve tear resistance and mitigate the effects of penetrating debris. Ultimately, we aim to develop a lab-scale test method to be used alongside modeling to more easily evaluate the efficacy of existing protection for the extremities and to develop and evaluate enhanced protection systems. Developing a better understanding of the thresholds and mechanisms of penetrating injuries to the extremities will provide essential data to support rapidly achievable, incremental, and pragmatic solutions that can reduce the extent and severity of extremity injury associated with explosively propelled soil and debris.

Poster Presentation by Dr. Marten Risling

Karolinska Institutet

Regrowth of Motor Nerves After Severe Injuries

Dr. Marten Risling,[17]Dr. Staffan Cullheim,[18]Dr. Thomas Carlstedt[19]

The capacity of motor and sensory nerve cells to survive and regrow axons after proximal injuries can be assumed to represent a limiting factor for successful reconstructions after severe

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[14] U.S. Army Research Laboratory.

[15] U.S. Army Research Laboratory.

[16] U.S. Army Research Laboratory.

[17] Karolinska Institutet.

[18] Karolinska Institutet.

[19] Karolinska Institutet.

limb injuries, such as blast injury. Road traffic accidents can result in avulsion injury of the spinal nerve roots. Such avulsions are usually located at the border between the central and peripheral nervous system, the site were the nerve roots emerge from the spinal cord. Spontaneous recovery cannot be expected after such injuries. In various experimental studies in rodents, cats, and nonhuman primates, it was shown that it was possible and useful to reconnect avulsed nerve roots with the spinal cord. Regrowing axons could indeed reinnervate limb muscles. These pre-clinical experiments initiated the development of a clinical treatment for cases of nerve root avulsions because of brachial plexus injuries. More than 20 years of experience of such treatment show that recovery and useful control of shoulder and elbow muscles is a possibility. The surgery should take place within weeks rather than months. Thus, motoneurons have a high capacity for survival and functional recovery, even after severe injuries.

Poster Presentation by Dr. Mark Suski

Los Robles Hospital

Novel Wound Debridement Devices to Enhance Limb Salvage

Dr. Mark Suski,[20]Dr. Neal M. Lonky[21]

Effective limb salvage and reconstruction may require significant wound care efforts that encompass both the acute and the chronic phase. The setting and resources available to achieve wound debridement during care may be a challenge. We will present case studies distinguishing the new technology over standard instruments: novel patented single-use, disposable fabric-based wound care brush curettage devices that can quickly and effectively clean and sample tissue surfaces. This FDA-cleared medical fabric provides versatility in case scenarios where either superficial debridement of slough or deep debridement of fibrotic tissue from chronicity or injury can be removed with a more patient-friendly approach. The fabric array can remove tissue for biopsy or culture by design. Limb salvage with ultimate reconstruction could be improved with versatile devices that address debridement of both surface and tunneling wounds.

Disclaimer

Dr. Lonky is the inventor of the devices discussed and an officer of Histologics LLC, manufacturer.

Poster Presentation by Dr. M. A. Hassan Talukder

Pennsylvania State University Center for Orthopaedic Research and Translational Science

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[20] Les Robles Hospital.

[21] University of California, Histologics LLC.

The Crushed Nerve Component of Blast Injury: Treatment

Dr. M. A. Hassan Talukder,[22] Dr. John Elfar,[23] Andrew Clark,[24] Dr. Chia George Hsu,[25] Dr. Mark Noble[26]

The Crushed Nerve Component of Blast Injury: 4-Aminopyridine promotes peripheral nerve recovery with enhanced global function, improved nerve conduction, decreased axonal degeneration, and increased myelination.

Traumatic peripheral nerve injury (TPNI) is a key component of blast injury and represents a major clinical problem that often leads to significant functional impairment and permanent disability. TPNIs are increasingly prevalent in combat-related extremity injuries and the common cause in combat is complex blast trauma in which some axonal continuity is maintained or there is complete nerve transection with extensive soft-tissue and bone injury. Despite the available modern diagnostic tests and advanced microsurgical techniques, most patients with TPNIs do not regain full motor or sensory function. Functional impairment with TPNI could be the result of a loss in axonal continuity, neuronal cell death, nerve demyelination, conduction defects, and/or muscle denervation. Therefore, there is an unmet need for new therapeutic strategies to promote the functional recovery in TPNI patients. 4-aminopyridine (4AP), an FDA-approved drug for the treatment of multiple sclerosis, has been shown to improve neuromuscular function in patients with diverse demyelinating disorders. We investigated the effect of 4AP on functional recovery, nerve conduction, axonal distribution, and nerve re-myelination during acute and chronic post-injury periods in mice whose sciatic nerves were crushed as would be seen in a blast injury but not severed. 4AP was delivered by intraperitoneal injection or localized sustained release vehicles or transdermally. We observed that 4AP promoted durable motor functional recovery of the limb with better preservation of axonal myelin sheath thickness, decreased axonal degeneration, and improved nerve conduction velocity in the crushed nerve. Importantly, the benefits with chronic 4AP are retained even after the treatment is stopped. These findings provide new insights into the therapeutic potential of 4AP in TPNI recovery especially as it relates to blast injury.

Disclaimer

This work was supported by grants from the NIH (K08 AR060164-01A) and DoD (W81XWH-16-1-0725), in addition to institutional support from the university.

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[22] Penn State Hershey College of Medicine.

[23] Penn State Hershey College of Medicine.

[24] The University of Rochester Medical Center.

[25] The University of Rochester Medical Center.

[26] The University of Rochester Medical Center.

APPENDIX A

Previous State-of-the-Science Meetings

1. International State-of-the-Science Meeting on Non-Impact, Blast-Induced Mild Traumatic Brain Injury, May 12–14, 2009, in Herndon, Va. https://blastinjuryresearch.amedd.army.mil/assets/docs/sos/meeting_proceedings/2009_SoS_Meeting_Proceedings.pdf
2. International State-of-the-Science Meeting on Blast Injury Dosimetry, June 8–10, 2010, in Chantilly, Va. https://blastinjuryresearch.amedd.army.mil/assets/docs/sos/meeting_proceedings/2010_SoS_Meeting_Proceedings.pdf
3. International State-of-the-Science Meeting on Blast-Induced Tinnitus, November 15–17, 2011, in Chantilly, Va. https://blastinjuryresearch.amedd.army.mil/assets/docs/sos/meeting_proceedings/2011_SoS_Meeting_Proceedings.pdf
4. International State-of-the-Science Meeting on the Biomedical Basis for Mild Traumatic Brain Injury Environmental Sensor Threshold Values, November 4–6, 2014, in McLean, Va. https://blastinjuryresearch.amedd.army.mil/assets/docs/sos/meeting_proceedings/2014_SoS_Meeting_Proceedings.pdf
5. International State-of-the-Science Meeting: Does Repeated Blast-Related Trauma Contribute to the Development of Chronic Traumatic Encephalopathy? November 3–5, 2015, in McLean, Va. https://blastinjuryresearch.amedd.army.mil/assets/docs/sos/meeting_proceedings/2011_SoS_Meeting_Proceedings.pdf
6. International State-of-the-Science Meeting: Minimizing the Impact of Wound Infections Following Blast-Related Injuries, November 29–December 1, 2016, in Arlington, Va. https://blastinjuryresearch.amedd.army.mil/assets/docs/sos/meeting_proceedings/2016_SoS_Meeting_Proceedings.pdf
7. International State-of-the-Science Meeting on the Neurological Effects of Repeated Exposure to Military Occupational Blast: Implications for Prevention and Health, March 12–15, 2018, in Arlington, Va. https://www.rand.org/pubs/conf_proceedings/CF380z1.html

APPENDIX B

Agenda of the Eighth Department of Defense International State-of-the-Science Meeting on Blast Injury Research

Tuesday, March 5, 2019

Time	Schedule	Presenter
8:00	Registration opens	
8:30	*Welcome*	Mr. Michael Leggieri Director, Blast Injury Research Coordinating Office
8:40	*Meeting Overview*	Dr. Charles Engel, RAND Corporation
8:50	*Keynote Address*	Dr. Joseph Caravalho, President and CEO, Henry M. Jackson Foundation
9:20	*Invited Presentations 1*	Mr. Stuart Campbell, Moderator
9:20	Defining Limb Salvage	Dr. Andrea Crunkhorn
9:40	Overview of DoD Limb Salvage Research	LTC(P) Joseph Alderete, U.S. Army
10:00	Advances in Surgical Research	Dr. Joseph Hsu
10:20	Q&A panel	Mr. Campbell
10:40	*AM BREAK*	
10:50	*Invited Presentations 2*	Dr. Christopher Dearth, Moderator
10:50	Advances in Reconstruction and Restoration Research	LTC(P) Benjamin Potter, U.S. Army
11:10	Advances in Adaptive, Robotic, and Other Technologies	Dr. Rory Cooper
11:30	Q&A panel	Dr. Dearth
11:45	*LUNCH AND POSTER SET-UP*	
1:15	*Invited Presentations 3*	Mr. Mike Galarneau, Moderator
1:15	Advances in Burn Reconstruction Research	Dr. Matthias Donelan
1:35	Advances in Rehabilitative Care Research	Dr. Paul Pasquina
1:55	RAND Literature Review Summary	Dr. Engel
2:15	Q&A for all speakers	Mr. Galarneau
2:35	*PM BREAK*	
2:50	*Scientific Presentations 1*	LTC Leon Nesti, U.S. Army, Moderator
2:50	Identification of a Combat-Related Limb Salvage Cohort	Dr. Stephen Goldman
3:10	Outcomes After Heel Pad Degloving Injuries	Dr. Michael Bosse
3:30	A Prospective RCT of Tissue Engineered Limb Salvage	Dr. Frank Lau
3:50	Beyond Limb Salvage: Orthoplastic Limb Restoration	LTC(P) Benjamin Potter
4:10	Q&A for all speakers	LTC Nesti
4:30	*Closing Remarks*	Mr. Leggieri, Dr. Engel
4:45	*Adjourn*	

Wednesday, March 6, 2019

Time	Schedule	Presenter
8:00	Registration opens	
8:20	*Welcome*	Mr. Leggieri
8:30	*Scientific Presentations 2*	Dr. Erik Wolf, Moderator
8:30	Characterization of Blast Injuries at a Civilian Trauma Center	Dr. Carl Nunziato
8:50	Acellular Fish Skin Graft	CDR (Ret.) Marvin Blake McBride III
9:10	PEG-Fusion Improves Recovery of Peripheral Nerve Injuries	Dr. Jaimie Shores
9:30	Using Regenerative Medicine to Repair Wounded Limbs	COL David Saunders
9:50	Speaker Q&As	Dr. Wolf
10:10	*AM BREAK*	
10:30	*Scientific Presentations 3*	Dr. Anne Ritter, Moderator
10:30	A Single-Shot Diagnostic for Nerve Injury in Mangled Limbs	Dr. John Elfar
10:50	Immune Directed Therapy to Prevent Heterotopic Ossification	Dr. Benjamin Levi
11:10	Nanoemulsion Against Drug-Resistant Wound Infections	Dr. Suhe Wang
11:30	Nerve Crush Injury Treatment: 4-Aminopyridine (4AP)	Dr. M. A. Hassan Talukder
11:50	Speaker Q&As	Dr. Ritter
12:10	*Working Group Roles and Responsibilities*	Dr. Engel
12:30	*LUNCH AND POSTERS*	
2:00	Break out to working groups*	Expert panelists
5:00	*Adjourn directly from working groups*	
	*Breaks determined within each working group	

Thursday, March 7, 2019

Time	Schedule	Presenter
8:00	Registration	
8:30	Break out to working groups*	
1:00	*LUNCH AND POSTERS*	
2:00	*Working Group Reports*	Dr. Engel, Moderator
2:00	Working Group A	Dr. Barbara Springer, Expert Panelist
2:20	Working Group B	Dr. Rory Cooper, Expert Panelist
2:40	Working Group C	Dr. James Ficke, Expert Panelist
3:00	Working Group D	Dr. Alberto Esquenazi, Expert Panelist
3:20	Working Group E	Dr. Joseph Hsu, Expert Panelist
3:40	Working Group F	Dr. Douglas Smith, Expert Panelist
4:00	*Closing Remarks and Adjourn*	Mr. Michael Leggieri
	*Breaks determined within each working group	

APPENDIX C

Keynote Speaker Biography

Dr. Joseph Caravalho, Jr., M.D.

Joseph Caravalho, Jr., M.D., is the president and chief executive officer of the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF). He leads an organization of 2,800 employees who support military medicine at locations across the United States and around the world.

Before joining HJF, Caravalho served as the Joint Staff surgeon at the Pentagon. As the chief medical adviser to the chairman of the Joint Chiefs of Staff, he provided recommendations to the chairman, the Joint Staff, and combatant commanders on a wide variety of medical and readiness issues.

Dr. Caravalho graduated in 1979 with a bachelor's degree in mathematics from Gonzaga University in Spokane, Washington. He was commissioned a second lieutenant through the Army Reserve Officers' Training Corps (ROTC) program. In 1983, he graduated with a medical doctorate from the Uniformed Services University of the Health Sciences (USUHS) F. Edward Hébert School of Medicine and was commissioned a captain in the Medical Corps. Clinically, he held positions as a staff internist, nuclear medicine physician, and cardiologist.

He served as chief of cardiology at Tripler Army Medical Center in Honolulu, Hawaii, and as deputy commander for clinical services at Womack Army Medical Center, Fort Bragg, North Carolina. His operational medical experience includes assignments as surgeon, 1st Battalion, 1st Special Forces Group (Airborne), Okinawa, Japan; physician augmented, Joint Special Operations Command, Fort Bragg; surgeon, 75th Ranger Regiment, Fort Benning, Georgia; deputy chief of staff, surgeon, U.S. Army Special Operations Command, Fort Bragg; and assistant chief of staff, health affairs, XVIII Airborne Corps, Fort Bragg.

Caravalho also commanded the 28th Combat Support Hospital and the 44th Medical Command (Rear) (Provisional), both at Fort Bragg. He had two deployments in support of OIF, most recently serving as the surgeon for both Multi-National Force-Iraq and Multi-National Corps-Iraq. He then served in succession as the commanding general for Southern Regional Medical Command and Brooke Army Medical Center; Northern Regional Medical Center; and the U.S. Army Medical Research and Materiel Command in Fort Detrick, Maryland. Before becoming the Joint Staff surgeon, he was the Army deputy surgeon general and deputy commanding general (support) of the U.S. Army Medical Command.

Dr. Caravalho is a graduate of the Command and General Staff College and the Army War College. He earned the Special Forces and Ranger tabs and was awarded the Expert Field

Medical Badge. He completed the Army Airborne and Flight Surgeon schools, as well as the Navy Dive Medical Officer and SCUBA courses.

His military awards include the Distinguished Service Medal with two Oak Leaf Clusters (2 OLC), Legion of Merit (OLC), Bronze Star Medal, Defense Meritorious Service Medal, Army Meritorious Service Medal (6 OLC), Joint and Army Commendation Medals, and the Army Achievement Medal (3 OLC). He also is a member of the Order of Military Medical Merit.

APPENDIX D

Biographies of Invited Speakers

Invited Speakers

This year, the SoSM hosted three invited-speaker presentation panels. Each panel was a moderated series of presentations involving knowledgeable researchers, military leaders, policymakers, and clinicians. The presentation panels were designed to create dialogue with the audience and among the panelists.

LTC(P) Joseph Alderete, Jr., M.D.

LTC Joseph F. Alderete, Jr., M.D., graduated from the United States Military Academy at West Point in 1997. He then attended medical school at Pennsylvania State College of Medicine and received his M.D. in 2001. He completed both his internship and residency in orthopedic surgery at Eisenhower Army Medical Center from 2001 to 2006. Following residency, he was a staff orthopedic surgeon at Reynolds Army Community Hospital from 2006 to 2008. He then attended the Mayo Clinic in Rochester, Minnesota, for a fellowship in musculoskeletal oncology. He moved on to Brooke Army Medical Center in San Antonio, Texas, where he is currently the chief of orthopedic oncology and the medical director for the Center for the Intrepid, Advanced Amputee and Limb Salvage Rehabilitation. He has had three combat deployments to Afghanistan, serving in positions from staff orthopedic surgeon to deputy commander for clinical services. His leadership positions include local, regional, and national roles, from associate program director for the San Antonio Uniformed Services Health Education Consortium (SAUSHEC) orthopedic surgery residency to Medical Board of Trustees for the Musculoskeletal Transplant Foundation. He has received many awards, military and academic, including the Warren R. Kadrmas Memorial Educator's Award for best teaching staff in 2013.

Dr. Rory A. Cooper, Ph.D.

Dr. Rory A. Cooper holds several positions, including associate dean for inclusion and Paralyzed Veterans of America Distinguished Professor of Rehabilitation Science and Technology and Orthopedic Surgery at the University of Pittsburgh. He is also the founding director and the VA Senior Research Career Scientist at the Human Engineering Research Laboratories at the University of Pittsburgh. He holds an adjunct professorship at the Robotics Institute at Carnegie Mellon University and is also a professor of physical medicine and rehabilitation at the USUHS in Bethesda, Maryland.

Cooper has published more than 300 peer-reviewed articles and three books, including *Care of the Combat Amputee*. He has more than 25 patents awarded or pending. Cooper's students have been the recipients of more than 50 national and international awards. A fellow of the National Academy of Inventors and other scholarly organizations, he is the recipient of the Secretary of Defense Meritorious Civilian Service Medal.

Cooper has served on federal advisory committees in the DoD, VA, and U.S. Department of Health and Human Services and is currently a member of the National Academy of Medicine's Committee on Assistive Products and Devices. As an Army veteran with a spinal cord injury, he won a bronze medal in the Paralympic Games in Seoul, South Korea, in 1988.

Cooper holds B.S. and M.Eng. degrees in electrical engineering from California Polytechnic State University, a Ph.D. in electrical and computer engineering with a concentration in bioengineering from the University of California at Santa Barbara, and an honorary doctorate from Xi'an Jiaotong University in China.

Dr. Andrea E. Crunkhorn, D.P.T.

As chief of clinical programs for the Extremity Trauma and Amputation Center of Excellence, Dr. Andrea Crunkhorn develops DoD policy, standards, and clinical consensus for limb trauma and amputation care. Recent efforts include the pending publication of a new chapter in Army Regulation 40-3 on prosthetic prescription; being a DoD Champion on the 2017 VA/DoD Clinical Practice Guideline for the Rehabilitation of the Individual with Lower Limb Amputation; and producing the 2017 Center for Medicare and Medicaid Services' Lower Limb Prosthetics Interagency Consensus Statement. Crunkhorn currently is developing consensus for outcomes measures, electronic health record note templates, and other clinician-level practice standardization efforts to ensure that beneficiaries receive the highest DoD standard.

Dr. Matthias B. Donelan

Dr. Matthias B. Donelan graduated from Harvard College in 1967 and received his medical degree from Tufts University School of Medicine in 1972 after spending an elective year as a student fellow in pathology. He received his surgical and plastic surgical training at Massachusetts General Hospital and subsequently spent an invaluable year as a plastic surgical tutor specialist with Sir William Manchester at the Middlemore Hospital in Auckland, New Zealand. Donelan is currently associate professor of surgery at Harvard Medical School and visiting surgeon at Massachusetts General Hospital. He has been chief of plastic surgery at the Boston Shriners Hospital since 1982 and is currently also the chief of staff.

Donelan is an expert in the field of burn reconstructive surgery and has developed numerous innovative techniques to enhance the care of burn patients. He has multiple publications in peer-reviewed scientific journals and has written definitive textbook chapters on burn reconstruction. He has long been an advocate for scar rehabilitation through tension relief and the use of phototherapy and advanced laser technologies. He is currently investigating fractional carbon dioxide laser treatment for aesthetic and reconstructive indications in burn and trauma patients. In addition to clinical and scientific activities, Donelan is involved in residency training and is the site director of the Harvard Combined Plastic Surgery Training Program at the Shriners Hospital for Children in Boston.

Dr. Joseph Hsu, M.D.

Joseph R. Hsu, M.D., is from Baton Rouge, Louisiana, and was an honor graduate from the United States Military Academy at West Point in 1994.

Hsu completed medical school, his residency in orthopedic surgery, and a fellowship in orthopedic trauma at Tulane University and Charity Hospital in New Orleans, Louisiana. He also completed limb deformity fellowships in Lecco, Italy, and Kurgan, Russia.

Hsu served in the U.S. Army and deployed in 2006 to Baghdad, Iraq. He spent the majority of his military career trying to optimize outcomes for limb-reconstruction patients and has translated that work to the civilian sector. Hsu also has focused his research and quality efforts on opioid prescribing safety and non-opioid strategies for pain management.

Hsu participated in the American Orthopaedic Association ABC Traveling Fellowship in 2017. He now lives in Charlotte, North Carolina, and is currently a professor of orthopedic trauma at Carolinas Medical Center and director of the Limb Lengthening and Deformity Service and vice chair of quality for the Atrium Health Musculoskeletal Institute.

Dr. Paul Pasquina, M.D.

COL (Ret.) Paul F. Pasquina, M.D., is a board-certified physiatrist with specializations in physical medicine and rehabilitation (PM&R), electrodiagnostic medicine, and pain medicine. After graduating from the United States Military Academy at West Point, he completed medical school at the USUHS followed by a residency in PM&R at Walter Reed National Military Medical Center and a fellowship in primary care/sports medicine at Georgetown University and the USUHS.

He currently serves as the chair of the Department of Rehabilitation Medicine and director of the Center for Rehabilitation Sciences Research at the USUHS. Additionally, he serves as the chief of the Department of Rehabilitation at Walter Reed National Military Medical Center.

LTC(P) Benjamin Potter, M.D.

LTC (Promotable) Benjamin "Kyle" Potter, M.D., FACS, currently serves as the director for surgery at Walter Reed National Military Medical Center and is a full professor in the Uniformed Services University–Walter Reed Department of Surgery. He is also the chief orthopedic surgeon for the Amputee Program at Walter Reed National Military Medical Center and a musculoskeletal oncology consultant at the National Institutes of Health.

Potter deployed to Afghanistan in 2011 and again in 2016, serving as the chief orthopedic Surgeon of the Task Force 115 Combat Support Hospital (Role III) at Camp Dwyer, Helmand Province, and subsequently with the 936th and 629th Forward Surgical Teams at FOB Fenty, Jalalabad Airfield, Nangarhar Province.

Potter is the immediate past president of the Society of Military Orthopaedic Surgeons. He has authored or coauthored more than 155 peer-reviewed publications, as well as numerous invited manuscripts and book chapters. He recently coedited the fourth edition of the *Atlas of Amputations and Limb Deficiencies* for the American Academy of Orthopaedic Surgeons and serves as a deputy editor for *Clinical Orthopaedics and Related Research* and an associate editor for the *Journal of Orthopaedic Trauma*.

Potter is an honor graduate of the United States Military Academy at West Point and an Alpha Omega Alpha graduate of the University of Chicago, Pritzker School of Medicine.

APPENDIX E

Expert Panel Biographies

An expert panel of six SMEs representing policymakers, clinicians, and scientists helped lead and focus discussions during the plenary sessions. The expert panel members also chaired working group sessions, in which participants addressed the five meeting questions.

Dr. Rory A. Cooper, Ph.D.

See Appendix D.

Dr. Alberto Esquenazi, M.D.

Dr. Alberto Esquenazi serves as chair of the Department of PM&R, director of the Gait and Motion Analysis Laboratory, clinical director of the Regional Amputee Center, and chief of the Prosthetic and Orthotic Clinic at Albert Einstein Medical Center in Philadelphia. Esquenazi is a professor of PM&R at Jefferson University School of Medicine and of biomedical engineering at Drexel University.

Esquenazi received his medical degree in medicine and surgery from Universidad Nacional Autonoma in Mexico City. He completed his residency in physical medicine and rehabilitation at the Temple/MossRehab program and a fellowship in gait analysis and prosthetic research at MossRehab in Philadelphia.

Esquenazi's research focuses on gait analysis, prosthetics, orthotics, spasticity, and robotics in rehabilitation. He has published widely in peer-reviewed journals and has authored more than 30 book chapters. He recently edited an issue of *PM&R* that focused on innovation impact on physical medicine and rehabilitation. His research and clinical work has led him to be an invited speaker at national and international events. He serves on the editorial boards for PM&R and the *Journal of NeuroEngineering and Rehabilitation*. He is an associate editor of two European journals.

Esquenazi is a member of national and international professional, educational, and research societies and review panels; he chaired the National Advisory Board on Medical Rehabilitation Research of the National Institute of Child and Human Development of the National Institutes of Health. He is a member of the board of the International Society of Physical and Rehabilitation Medicine and president-elect of the American Academy of Physical Medicine and Rehabilitation. He is the recipient of prestigious national and international

awards for his clinical, research, and educational efforts and has been recognized for several years among "Top Doctors" in Philadelphia and as one of "America's Top Doctors."

Dr. James Ficke, M.D., F.A.C.S.

COL James Ficke, M.D., F.A.C.S., is the Robert O. Robinson Professor of Orthopaedic Surgery at the Johns Hopkins School of Medicine and director of the Department of Orthopaedic Surgery. He is also orthopedist-in-chief of the Johns Hopkins Hospital. He is nationally renowned as an expert on the treatment of complex foot and ankle patients, lower-extremity trauma patients, and amputees.

Ficke received his M.D. from the USUHS in 1987. He completed a transitional internship at Madigan Army Medical Center and finished his residency in orthopedic surgery at Tripler Army Medical Center. He also completed an AO fellowship in Trauma in Munich, Germany, and a foot and ankle fellowship in Dallas, Texas.

Prior to his current position, Ficke was chair of the Department of Orthopaedics and Rehabilitation at the San Antonio Military Medical Center. He also served the U.S. Army Surgeon General as the senior adviser on policy and personnel for orthopedics and extremity injuries for seven years.

During his deployment as deputy commander of clinical services at the 228th Combat Support Hospital in Mosul, Iraq, from 2004 to 2005, he was the senior orthopedic surgeon, treating more than 600 U.S. soldiers and Iraqi patients for war injuries.

Ficke has received numerous awards for his skills as a surgeon and educator, as well as two dozen military decorations and awards, including the Bronze Star and Meritorious Service Medals. His service earned him the Society of Military Orthopaedic Surgeons' prestigious 2010 Colonel Brian Allgood Memorial Leadership Award, and the Surgeon General's 2010 Major General Lewis Aspey Mologne Award.

He has served as the co-chair of the Extremity War Injury Symposium sponsored by the American Academy of Orthopaedic Surgeons since 2005.

Dr. Joseph Hsu

See Appendix D.

Dr. Douglas Smith, M.D.

Dr. Douglas Smith, M.D., is a board-certified orthopedic surgeon. He completed medical school at the University of Chicago Pritzker School of Medicine, followed by an internship and residency in the Department of Orthopaedics and Rehabilitation at Loyola University Medical Center and a fellowship in Foot, Ankle, and Amputation Surgery at Harborview Medical Center at the University of Washington. Smith serves as a professor in the Department of Rehabilitation Medicine and is the Henry M. Jackson Foundation for the Advancement of Military Medicine's chief orthopedic adviser for the Center for Rehabilitation Sciences Research (CRSR) at the USUHS. In his current role within CRSR, Smith directs the research

team to conduct research studies that seek to evaluate and improve on current standard-of-care rehabilitation/prosthetics and assess the viability and efficacy of new treatments and products that aim to better support the population of individuals with traumatic limb loss. Smith also provides consultation and education within the Department of Rehabilitation at Walter Reed National Military Medical Center.

COL (Ret.) Barbara Springer, P.T., Ph.D.

COL (Ret.) Barbara Springer is the director of operations for the 501(c)3 Quality of Life Plus (QL+) program. Its mission is to foster and generate innovations that aid and improve the quality of life for those who have served in the military. She also serves as a research physical therapist working with amputees at Walter Reed National Military Medical Center. She is board-certified orthopedic and a sports physical therapy (PT) specialist.

Springer served 25 years in the U.S. Army and retired out of the Office of the Surgeon General, where she was the director of the Rehabilitation and Reintegration Division. She recommended policy and instituted Army-wide standards of care for rehabilitation and transition of wounded, ill, and injured soldiers. Before assuming this position, Springer was the chief of integrated PT services, where she served as leader to both Walter Reed Army Medical Center and the National Naval Medical Center in the Washington, D.C., metro area. In this role, she ensured world-class rehabilitative care for thousands of wounded service members and other military beneficiaries, averaging more than 7,000 visits each month. She was also responsible for conducting, tracking, and supervising clinical research projects; overseeing graduate education; supporting congressional projects; supporting amputee, traumatic brain injury, and spine centers; and planning for and executing PT service integration for Base Realignment and Closure. While serving in this position, Springer was also the White House PT consultant, the North Atlantic Regional Medical Command PT consultant, and a member of the Military Amputee Research Program Executive Committee.

APPENDIX F

Planning Committee

This meeting was made possible thanks to the guidance, planning, and insights of the members of the planning committee of the eighth SoSM:

Stuart Campbell
Extremity Trauma and Amputation Center of Excellence

Dr. Jill Cancio
Extremity Trauma and Amputation Center of Excellence, Center for the Intrepid

Dr. Rory Cooper
University of Pittsburgh

Dr. Andrea Crunkhorn
Extremity Trauma and Amputation Center of Excellence

Dr. Christopher Dearth
Extremity Trauma and Amputation Center of Excellence

CAPT Eric Elster
Uniformed Services University of the Health Sciences

Dr. Alberto Esquenazi
Albert Einstein Medical Center, Jefferson University School of Medicine, and Drexel University

Dr. Mike Galarneau
Naval Health Research Center

COL Brandon Goff
Center for the Intrepid

MAJ David Kingery
U.S. Army Institute of Surgical Research

Dr. Joe Miller
Extremity Trauma and Amputation Center of Excellence

LTC Keith Myers
Walter Reed National Military Medical Center

LTC Leon Nesti
Uniformed Services University/U.S. Army Medical Research and Development Command

Dr. Benjamin Potter
Walter Reed National Military Medical Center

Dr. Lloyd Rose
U.S. Army Medical Research and Development Command, Clinical and Rehabilitative Medicine Research Program

Dr. Daniel Stinner
Vanderbilt University Medical Center, Department of Orthopaedic Surgery

Dr. Erik Wolf
U.S. Army Medical Research and Development Command

Dr. Anne Ritter
U.S. Army Medical Research and Development Command, Combat Casualty Care Research Program

APPENDIX G

Meeting Participants

Dr. Joe Abdo
PolarityTE

Dr. Denes Agoston
Uniformed Services University of the Health Sciences

LTC Joseph Alderete
Joint Base San Antonio

Dr. Vlado Antonic
Walter Reed Army Institute of Research, Wound Infection Department

Robert Bahr
Walter Reed National Military Medical Center

Dr. James Baker, Jr.
University of Michigan

Elizabeth Barrows
Independent consultant

James Batchelor
University of Southampton

Cynthia Bodner
U.S. Marine Corps

Dr. Michael Bosse
Atrium Health, Carolinas Medical Center

Dr. Warren Breidenbach
Air Force Institute for Research and Medicine Engineering and Defense 59th

Dr. Timothy Brindle
Veterans Affairs Office of Research and Development

Dr. Kelley Brix
Defense Health Agency

Dr. Jeremy Brown
National Institutes of Health

Edward Brown
U.S. Army Medical Materiel Development Command

Dr. Rebecca Brown
University of Southampton

Dr. Jeffrey Brown
AlloSource—Innovation Center

Stuart Campbell
Extremity Trauma and Amputation Center of Excellence, U.S. Army Medical Command

Dr. Joseph Caravalho, Jr.
Henry M. Jackson Foundation for the Advancement of Military Medicine

LTC Robert Carter
Program Executive Office for Simulation, Training and Instrumentation

Emily Casarona
Military Service Initiative, George W. Bush Institute

Dr. Namas Chandra
New Jersey Institute of Technology

Franco Ciammachilli
Office of the Assistant Secretary for Preparedness and Response

Dr. Mary Clouser
Naval Health Research Center

Dr. Rory Cooper
University of Pittsburgh

Dr. Andrea Crunkhorn
Extremity Trauma and Amputation Center of Excellence

LTC Jean-Claude D'Alleyrand
Walter Reed National Military Medical Center

Dr. Gregory Davenport
The Conafay Group

CAPT (Ret.) Timothy Davis
Uniformed Services University of the Health Sciences

Dr. Alan Davis
Baylor College of Medicine, Center for Cell and Gene Therapy

Dr. Elizabeth Davis
Baylor College of Medicine, Center for Cell and Gene Therapy

Dr. Wendy Dean
Henry M. Jackson Foundation for the Advancement of Military Medicine

Dr. Christopher Dearth
Walter Reed National Military Medical Center/ Uniformed Services University of the Health Sciences

Dr. Jack Denny
University of Southampton

Dr. Matthias Donelan
Shriners Hospital for Children

CDR Josh Duckworth
Uniformed Services University of the Health Sciences

Dr. John Elfar
Pennsylvania State University, Center for Orthopaedic Research and Translational Science

Kate Eltzroth
Martin-Blanck Associates

Dr. Susan Eskridge
Naval Health Research Center, Department of Medical Modeling, Simulation and Mission Support

Dr. Alberto Esquenazi
Albert Einstein Medical Center, Jefferson University School of Medicine, and Drexel University

Dr. Ivy Estabrooke
PolarityTE, Inc.

Dr. James Ficke
Johns Hopkins Medicine

CAPT Mark Fleming
Navy Trauma Training Center

CAPT Jonathan Forsberg
Walter Reed National Military Medical Center

Mike Galarneau
Naval Health Research Center

Maj Cubby Gardner
Combat Casualty Care Research Program

Brittany Garry
Walter Reed Army Institute of Research

Dr. Aarti Gautam
U.S. Army Center for Environmental Health Research

Dr. Stephen Goldman
Extremity Trauma and Amputation Center of Excellence

Dr. Vijay Gorantla
Wake Forest Institute for Regenerative Medicine

Renee Greer
Defense Health Agency Joint Trauma System

Dr. Raj Gupta
U.S. Department of Defense Blast Program Coordinating Office

Dr. Rasha Hammamieh
U.S. Army Center for Environmental Health Research

Dr. Brad Hendershot
Walter Reed National Military Medical Center/Uniformed Services University of the Health Sciences

Leticia Hopkins
U.S. Army Medical Research and Development Command

COL Miguel Howe
George W. Bush Institute

Dr. Joseph Hsu
Carolinas Medical Center and Atrium Health Musculoskeletal Institute

CDR Eric Hui
RAND Corporation

Cheryl Hull
Henry M. Jackson Foundation

Janelle Hurwitz
Office of the Assistant Secretary for Preparedness and Response

Elizabeth Husson
Walter Reed National Military Medical Center

Dr. Narayan Iyer
Office of the Assistant Secretary for Preparedness and Response

Michelle Jamin
Elon University

Dr. Jelena Janjic
Duquesne University School of Pharmacy

MAJ Brian Johnson
Walter Reed Army Institute of Research

Dr. Michael Kleinberger
U.S. Army Research Laboratory

Dr. Todd Kuiken
Shirley Ryan Ability Lab

Dr. Anna Kushnir
Strategic Marketing Innovations

Dr. Sanjiv Lalwani
Lynntech, Inc.

Dr. Frank Lau
Louisiana State University Health Sciences Center New Orleans

MAJ Leigh Anne Lechanski
MATC Physical Therapy

Michael Leggieri
U.S. Department of Defense Blast Injury Research Program Coordinating Office

Dr. Benjamin Levi
Michigan Medicine, University of Michigan

Dr. Kathryn Loftis
United States Army Research, Development and Engineering Command

Dr. Neal Lonky
University of California/MediTech Development Inc.

Dr. George Ludwig
U.S. Army Medical Research and Development Command

CDR (Ret.) Blake McBride
Kerecis LLC

Justin McKee
U.S. Army Research Laboratory

Maria Medina
Walter Reed Army Institute of Research

Dr. Catriona Miller
U.S. Air Force School of Aerospace Medicine

Seileen Mullen
Martin, Blanck & Associates

Dr. Vijaya Prakash Muthaiah
University at Buffalo

LTC Keith P. Myers
Walter Reed National Military Medical Center

CAPT George Nanos
Walter Reed National Military Medical Center

Dr. Jennifer Neff
Allvivo Vascular

LTC Leon Nesti
Uniformed Services University of the Health Sciences

Dr. Carl Nunziato
University of Texas at Austin

Dr. Paul Pasquina
Uniformed Services University of the Health Sciences/Walter Reed National Military Medical Center

Dr. Brian Pfister
The Conafay Group

Ir. Mathieu Philippens
Netherlands Organization for Applied Scientific Research

Dr. Thuvan Piehler
U.S. Army Medical Research and Development Command/Military Operational Medicine Research Program

LTC(P) Benjamin Potter
Walter Reed National Military Medical Center

Dr. Lisa Prasso
U.S. Department of Defense

Dr. Jaques Reifman
Biotechnology High Performance Computing Software Applications Institute/Telemedicine and Advanced Research Technology Center

Dr. Marten Risling
Karolinska Institutet

Dr. Anne Ritter
U.S. Army Medical Materiel Development Command

Dr. Akua Roach
Congressionally Directed Medical Research Programs

Dr. Nicholas Robbins
AirMed Program

COL David Saunders
U.S. Army Medical Materiel Development Command

LTC Matthew Scherer
U.S. Army Medical Materiel Development Command

Dr. Deborah Shear
Walter Reed Army Institute of Research

Dr. Paul Sheehan
Defense Advanced Research Projects Agency

John Shero
Extremity Trauma and Amputation Center of Excellence

Dr. Jaimie Shores
Johns Hopkins University

Cindy Smith
Army Public Health Center

Dr. Douglas Smith
Department of Rehabilitation Medicine; Henry M. Jackson Foundation for the Advancement of Military Medicine in support of the Center for Rehabilitation Sciences Research

Maj Brian Smith
Air Force Medical Support Agency

LCDR Jason Souza
Walter Reed National Military Medical Center

COL (Ret.) Barbara Springer
Henry M. Jackson Foundation for the Advancement of Military Medicine

Dr. Mark Suski
Los Robles Hospital

Dr. M. A. Hassan Talukder
Pennsylvania State University Center for Orthopaedic Research and Translational Science

Terri Tanielian
RAND Corporation

Jerika Taylor
Henry Jackson Foundation in support of the Center for Rehabilitation Sciences Research

Amanda Toman
Combating Terrorism Technical Support Office

LTC Stuart Tyner
Walter Reed Army Institute of Research

Dr. Suhe Wang
University of Michigan, Ann Arbor

Dr. David Weiss
University of Virginia

Dr. Therese West
Combat Casualty Care Research Program

Dr. J. Kenneth Wickiser
United States Military Academy

Dr. Erik Wolf
U.S. Army Medical Materiel Development Command

Wayne Young
Biomedical Advanced Research and Development Authority

Dr. Mariusz Ziejewski
North Dakota State University

Dr. Barbara Zoretic
Walter Reed National Military Medical Center, Department of Rehabilitation

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