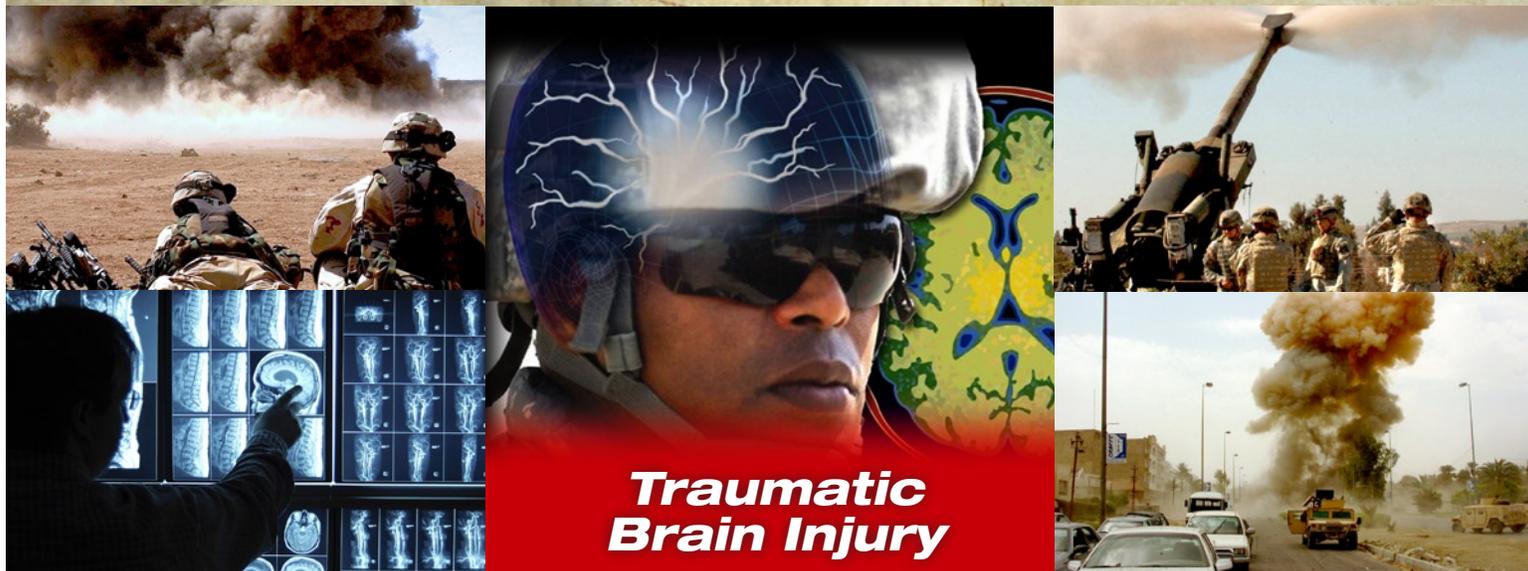

Summary of Meeting Proceedings



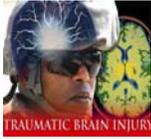
**Traumatic
Brain Injury**

International
**State-of-
the-Science**
Meeting on

Non-Impact, Blast-Induced Mild Traumatic Brain Injury



May 12–14, 2009
Hyatt Dulles, Herndon, VA



**International State-of-the-Science Meeting on Non-Impact,
Blast-Induced Mild Traumatic Brain Injury**
Hyatt Dulles, Herndon, Virginia, May 12–14, 2009



PREFACE

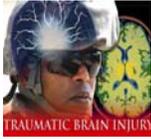
It is my pleasure to acknowledge the staffs of the DoD Blast Injury Research Program Coordinating Office and the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury for their work to plan and implement the International State-of-the-Science Meeting on Non-Impact Blast-Induced Mild Traumatic Brain Injury. They successfully assembled subject matter experts from the science, engineering, and health care disciplines to address the critically-important topic of the existence and mechanisms of non-impact, blast-induced mild traumatic brain injury (mTBI).

I wish to commend the meeting presenters, panel members, and attendees for their excellent contributions, both in their presentations and discussions. Without their active participation, it would not have been possible to critically assess the state of scientific knowledge. I thank all investigators who have conducted research that provides vital evidence needed to prevent, mitigate, and treat blast-related brain injuries. Further, I urge scientists to continue relevant programs of research and instigate novel studies that will answer compelling research questions.

The purpose of this document is to summarize the proceedings of the meeting and to disseminate information regarding what is known and what still needs to be learned about non-impact, blast-induced mTBI to a broad audience, including scientists, engineers, medical researchers, health care professionals, protection system development experts, and military leaders and decision-makers at all levels.

Thank you for your contributions to make this meeting a great success.

John F. Glenn, Ph.D.
Senior Executive Service
Director, U.S. Army Medical Research and
Materiel Command



**International State-of-the-Science Meeting on Non-Impact,
Blast-Induced Mild Traumatic Brain Injury**
Hyatt Dulles, Herndon, Virginia, May 12–14, 2009



SUMMARY OF MEETING PROCEEDINGS

INTRODUCTION

The Department of Defense (DoD) Blast Injury Research Program Coordinating Office (PCO), in coordination with the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury, hosted the International State-of-the-Science Meeting on Non-Impact, Blast-Induced Mild Traumatic Brain Injury on May 12–14, 2009, to critically examine research focused on the relationship between blast exposure and non-impact blast-induced mild traumatic brain injury (mTBI) and to review proposed injury mechanisms.

The meeting was attended by over 75 experts representing the DoD, the Department of Transportation, the Department of Veterans Affairs, academia, and industry. Countries represented at the meeting included Canada, Japan, the Netherlands, Sweden, and the United States.

This document summarizes the proceedings of the meeting. The PCO is writing a more detailed review and will submit it to a peer-reviewed journal for publication.

METHOD

The first day-and-a-half of the meeting consisted of a series of 27 short presentations by scientists who study non-impact, blast-induced mTBI. A diverse array of research topics was presented, ranging from blast physics and mathematical modeling to animal modeling and neurocognitive studies in humans. A four-member panel of accomplished and respected scientists (see below) listened to each presentation and stimulated post-presentation discussions. On the afternoon of the second day, participants divided into four workgroups. A panel member facilitated workgroup discussions. Workgroup members were charged to discuss and answer four specific questions based on their knowledge and the material presented at the meeting. Following ample time for workgroup discussion, the participants reconvened and each panel member briefed the conclusions of his panel. A general discussion concluded the open portion of the meeting. Panel members and Blast PCO staff met for a closed executive session on day three to synthesize information from the meeting and to formulate the findings and recommendations presented in this summary.

The panel consisted of the following individuals:

- Colonel Karl E. Friedl, Ph.D. (Panel Chair), Director, Telemedicine and Advanced Technology Research Center, U.S. Army Medical Research and Materiel Command
- John D. Joannopoulos, Ph.D., Francis Wright Davis Professor of Physics, Massachusetts Institute of Technology, and Director, Institute for Soldier Nanotechnologies
- Steven G. Kaminsky, Ph.D., Vice President of Research, Uniformed Services University of the Health Sciences
- Erik G. Takhounts, Ph.D., Office of Applied Vehicle Safety Research, Human Injury Research Division, National Highway Traffic Safety Administration

The meeting participants were charged with answering the following questions during the workgroup sessions:

- Is non-impact blast exposure associated with a physical mTBI?
- If so, is there substantial evidence to support one mechanism as the most plausible explanation for how non-impact blast exposure is associated with mTBI?
- What research questions warrant further study and will close the knowledge gaps regarding any association between non-impact blast exposure and mTBI?
- How can researchers standardize research methods to facilitate research synthesis of comparable studies?

FINDINGS

Mild TBI is currently defined by the event and through self-report of symptoms. The working definition is any post-event exposure alteration of mental state at the time of injury, any loss of consciousness lasting 30 minutes or less, or post-traumatic amnesia lasting less than 24 hours. There is agreement that this definition does not meet the needs for clinical assessment of brain injury.

Based on data presented at the meeting and other published and unpublished studies, there is evidence from clinical and animal studies that non-impact, blast-induced mild trauma to the brain can occur. The findings include:

- Statistically significant differences in Diffusion Tensor Imaging-Based Fractional Anisotropy between Service Members with documented mTBI associated with blast and Service Members with impact-only mTBI.
- Statistically significant differences in Event-Related Potentials between blast and non-blast exposures in human studies.
- Preliminary evidence of disturbed phase synchrony following blast exposure.
- Differences in functional magnetic resonance imaging (fMRI) between Breacher instructors and students (statistically significant fMRI results, non-statistically significant neurocognitive results).
- Alterations in inflammatory markers in animal studies.
- Physiological, histological, and/or behavioral differences between blast and non-blast exposures in shock tubes with rodents.
- Low-level axonal, neuronal, and/or glial damage/reactivity in blast studies (including free field and other) in porcine models.

These findings are particularly relevant given the improved survivability due to protection of the torso by body armor. Several studies have demonstrated that body armor provides protection against primary blast effects to the lungs and other air-filled organs, which are usually the first affected systems in a blast.

There are limitations to the observations highlighted above, including:

- Clinical studies are limited by a small sample size. They also lack detailed information regarding exposure conditions at the time of injury.
- Translation of findings from animal studies to humans is limited by the uncertainty of scaling relationships, as well as biological and behavioral differences.
- Laboratory exposures that produce brain injury in animals are limited by the lack of knowledge of real-world exposure conditions.

There is insufficient evidence to support one mechanism of insult and one physiological response as the most plausible explanation for the association of non-impact blast exposure with mTBI. Blast insults include shock waves, toxic gases, thermal injuries, electromagnetic pulses, and acceleration. Biophysical responses include biomechanical (e.g., strain rates, stresses, flexures), chemical, vascular surge, cavitation, and shock wave-induced piezoelectric electromagnetic alterations. Physiological responses include vasospasm, hemorrhage/micro-bleeds, intracranial pressure, neuronal damage (synaptic, dendritic, cell body), inflammatory responses, and alterations in neurotransmitters.

There are insufficient data on the nature of non-impact, blast-induced mTBI to make recommendations on how to better protect soldiers. Hence, there is a need to assess and leverage neurobiological, neurobehavioral, and biophysical research funded by the DoD's Traumatic Brain Injury/Post-Traumatic Stress Disorder program and other federal programs that pertain to this topic.

KNOWLEDGE GAPS

There are knowledge gaps regarding the association between non-impact blast exposure and mTBI. These gaps, and potential actions to pursue, include:

- **Components and thresholds of a blast responsible for the insult and injury.**
 - Quantify real-world blast exposures.
 - Develop more effective exposure-monitoring technologies.
 - Identify injuries specifically associated with individual components of the blast wave.
 - Determine the biomechanics of injury response and tolerance and the injury response mechanism.
 - Understand synergies among primary/secondary/tertiary blast injuries.
 - Collect epidemiological data surrounding in-theater blast events and assess outcomes.
- **Clinical correlates associated with non-impact blast exposure.**
 - Model in vitro and in vivo cellular susceptibility to mechanical stress conditions.
 - Clarify the pathophysiology in laboratory/computational modeling and clinical experiments.
 - Develop a mouse model of mTBI to enable the construction of transgenics.
 - Elucidate the effect and susceptibility to multiple blast exposures.
 - Elucidate the effect of predisposing factors (e.g., environmental stressors, high arousal state, polytrauma).
 - Develop scaling relationships for animal models and validate models for human injury.
 - Identify predictors of individual differences in responses to blast exposure.
- **Validated computational and analytic models.**
 - Develop accurate high-rate constitutive models for tissue response and cavitation phenomena.
 - Develop methodologies for multiscale modeling for coupling biomechanics and pathophysiology.
 - Develop methodologies to couple electromagnetic and mechanical dynamics in piezoelectric systems.
- **Neuropathological data surrounding blast injury in humans.**
 - Delineate the pathology of mTBI.

- Delineate the pathology of the spectrum of moderate TBI.
- Develop in vivo methodologies that correlate with the histopathology (e.g., MRI, serum biomarkers, neuropsychological).
- Reduce the time lag from injury in theater to postmortem examination of brain tissue.
- **Sharing of data across research entities.**
 - Develop a database to help validate/refute models (e.g., The Autism Consortium).
 - Provide open access of data to the community at large.
 - Transition existing datasets to an electronic database.
 - Standardize input to the database.
- **Recovery of historical blast injury research data.**
 - Migrate existing paper datasets to an electronic database.
- **Scientifically informed protection, prevention, and treatment strategies for blast-related mTBI.**
 - Develop biomedically valid injury criteria based on biomechanical and/or physiological injury mechanisms that can be used to guide the development of effective protection equipment.

RECOMMENDATIONS

- Standardize research methods to facilitate research synthesis of comparable studies.
- Encourage detailed documentation of experimental and modeling work.
- Establish a data repository or atlas of studies for researchers to compare across models.
- Encourage dissemination of findings in peer-reviewed literature.
- Support the recommendation to adopt common data elements on brain injury and psychological health.
- Develop a simple, far-forward evaluation platform (including balance, hearing, smell, and oculometrics) that can be implemented immediately after a blast event.
- Encourage research interactions between clinicians, engineers, and other disciplines.
- Emphasize the importance of the inclusion of proper control groups and protective equipment in experimental design.
- Create specialized Integrated Product Teams to periodically review emerging findings and make recommendations for research and clinical practice.

APPENDICES

- A. Welcome Letter
- B. Meeting Agenda
- C. Meeting Participants
- D. Office Contact Information

A

WELCOME LETTER

Dear Colleague,

On behalf of the DoD Executive Agent for Medical Research for Prevention, Mitigation and Treatment of Blast Injury, welcome to the International State-of-the-Science Meeting on Non-Impact, Blast-Induced Mild Traumatic Brain Injury (mTBI). Approximately 80 subject matter experts volunteered to participate in this meeting and I look forward to the important work that we will accomplish. Ultimately, the scientific knowledge gained from this meeting will guide efforts to prevent combat, occupational, and other traumatic injuries and may inform clinicians how to treat those with existing traumatic brain injury.

Non-impact blast exposures occur when Warfighters are close enough to an explosion to experience the high pressures created by the blast itself but far enough away to avoid penetrating injuries caused by fragments and blunt impact injuries caused by debris or by whole-body translation. The existence and mechanism of a non-impact, blast-induced mTBI remain key knowledge gaps in the DoD Blast Injury Research Program. Understanding the mechanism of any injury is key to developing effective prevention, mitigation, and treatment strategies.

The current DoD blast injury research portfolio consists of nearly 50 ongoing research projects that are studying non-impact, blast-induced mTBI. These projects are investigating many possible injury mechanisms, including a blast-induced surge in the vascular system, direct effects of the blast pressure wave on the brain tissue, head acceleration, electromagnetic pulse, thermal effects, and inhaled toxic gases. These studies are critically important because without conclusive data, it would be unwise to modify existing protection systems, such as body armor and combat helmets. Uninformed modifications of any protection systems could have disastrous results.

This meeting will critically examine research about the relationship between blast exposure and non-impact, blast-induced mTBI and review proposed injury mechanisms. Your active participation is critical to answering the following questions:

1. Is non-impact blast exposure associated with a physical mTBI?
2. If so, is there substantial evidence to support one mechanism as the most plausible explanation for how non-impact blast exposure is associated with mTBI?
3. What research questions warrant further study, and will close the knowledge gaps regarding any association between non-impact blast exposure and mTBI?
4. How can researchers standardize research methods to facilitate research synthesis of comparable studies?

Please accept my gratitude for your active participation in this meeting.

Michael J. Leggieri, Jr.
Director, DoD Blast Injury Research
Program Coordinating Office

B**MEETING AGENDA****Tuesday, May 12, 2009**

| | | | |
|----------|--|---|---------|
| 7:30 AM | Registration/Continental Breakfast | | |
| 8:00 AM | Introduction | Mr. Michael Leggieri DoD Blast Injury Research Program Coordinating Office | Room AB |
| 8:30 AM | Overview of TBI in the DoD | Col (sel) Michael Jaffee Defense and Veterans Brain Injury Center | Room AB |
| 8:50 AM | Blast 101: Basics of Blast Physics | Dr. David Ritzel Dyn-FX Consulting Ltd. | Room AB |
| 9:20 AM | A Mathematical Model Coupling Biomechanics, Neuroexcitation, Astrocyte Swelling, and Perfusion in Mild TBI | Dr. Andrzej Przekwas CFD Research Corp. | Room AB |
| 9:40 AM | Exposition/Effects Relations: The Foundation for Computer Modeling and the Establishment of Injury/Safety Criteria | Dr. Mårten Risling Karolinska Institutet | Room AB |
| 10:00 AM | Break | | |
| 10:20 AM | Biofidelic Models and Large-Scale Simulation for Blast-Related Traumatic Brain Injury Physics and Mitigation | Dr. Raul Radovitzky Massachusetts Institute of Technology | Room AB |
| 10:40 AM | Blast-Induced Traumatic Brain Injury Research at Lawrence Livermore National Laboratory | Dr. Willy Moss/Dr. Michael King Lawrence Livermore National Laboratory | Room AB |
| 11:00 AM | Investigation of Acceleration-Induced mTBI in Rats | Dr. Paul Rigby L-3 Communications/Jaycor | Room AB |
| 11:20 AM | Working Toward Mechanism-Based Blast-Induced TBI Thresholds | Dr. Amy Courtney United States Military Academy | Room AB |
| 11:40 AM | Blast-Induced Electromagnetic Fields in the Brain | Dr. Steven Johnson Massachusetts Institute of Technology | Room AB |
| 12:00 PM | Lunch – Historical Perspectives on Blast TBI: What Have We Not Learned? | | |
| 1:10 PM | Characterization of a New Rodent Model of Blast-Induced Brain Injury | Dr. Douglas DeWitt University of Texas Medical Branch | Room AB |
| 1:30 PM | Developing a Military-Relevant Experimental Model and Identifying the Essential Interactive Pathways between Blast and the Brain | Dr. Ibolja Cernak Johns Hopkins University Applied Physics Laboratory | Room AB |
| 1:50 PM | Preliminary Autopsy Neuropathology Observations from Military Personnel with a History of Possible mTBI | Dr. Vernon Armbrustmacher Armed Forces Institute of Pathology | Room AB |

Tuesday, May 12, 2009 (cont.)

| | | | |
|---------|--|---|---------|
| 2:10 PM | MRI Studies of Brain Alterations in Mild TBI and PTSD | Dr. Norbert Schuff San Francisco Veterans Affairs Medical Center | Room AB |
| 2:30 PM | Blast-Induced Mild Traumatic Brain Injury | Dr. Cindy Bir/Dr. Albert King Wayne State University | Room AB |
| 2:50 PM | Break | | |
| 3:10 PM | What Is the Strength of Association Between a History of Blast Mechanism and Persistent Post-Concussive Symptoms? What is the Optimal Risk Communication Strategy? | COL Charles Hoge Walter Reed Army Institute of Research | Room AB |
| 3:30 PM | Enhanced Measurement of Disrupted Functional Connectivity in the Brain after Blast Injury | Dr. Scott Sponheim University of Minnesota | Room AB |
| 3:50 PM | Neural Correlates of Major Depression in Soldiers with a History of Blast Exposure | Dr. Scott Matthews University of California, San Diego | Room AB |
| 4:10 PM | Neurocognitive Sequelae of OEF/OIF Blast-Induced TBI | Dr. Larry Tupler Duke University | Room AB |
| 4:30 PM | Diffusion Tensor Imaging and mTBI – A Case-Control Study of Blast (+) in Returning Service Members Following OIF and OEF | Dr. David Moore Defense and Veterans Brain Injury Center | Room AB |
| 4:50 PM | Wrap Up | Col (sel) Marla De Jong DoD Blast Injury Research Program Coordinating Office | Room AB |

Wednesday, May 13, 2009

| | | | |
|---------|--|--|---------|
| 7:30 AM | Continental Breakfast | | |
| 8:00 AM | Administration and Goals for the Day | Mr. Michael Leggieri DoD Blast Injury Research Program Coordinating Office | Room AB |
| 8:10 AM | Understanding Shock Wave Transmission to the Brain | Dr. Pamela VandeVord Wayne State University | Room AB |
| 8:30 AM | DARPA's Blast Program – Preventing Violent Explosive Neurologic Trauma (PREVENT) | COL Geoffrey Ling Defense Advanced Research Projects Agency | Room AB |
| 8:50 AM | Blast-Induced Brain Injury in Animal Models | Dr. Annette Säljö University of Gothenburg | Room AB |
| 9:10 AM | Mild TBI: Myths and Mayhem | Dr. Douglas Smith University of Pennsylvania | Room AB |
| 9:30 AM | Survival/Lethality Criterion for Primary Blast Brain Trauma | Dr. Cameron Dale Bass University of Virginia | Room AB |
| 9:50 AM | Break | | |

Wednesday, May 13, 2009 (cont.)

| | | | |
|----------|---|--|------------|
| 10:10 AM | Blast Overpressure in Rats: Recreating a Battlefield Injury in the Laboratory | Dr. Joseph Long Walter Reed Army Institute of Research | Room AB |
| 10:30 AM | Assessment of Blast: NMRC Perspectives | Dr. Stephen Ahlers Navy Medical Research Center | Room AB |
| 10:50 AM | Orientation to Workgroups | Mr. Michael Leggieri DoD Blast Injury Research Program Coordinating Office | Room AB |
| 11:10 AM | Lunch | | |
| 12:10 PM | Workgroups | | A, B, C, D |
| 2:10 PM | Break | | |
| 2:30 PM | Workgroups | | A, B, C, D |
| 3:30 PM | Brief Back – Workgroup 1 | Dr. John Joannopoulos Massachusetts Institute of Technology | Room AB |
| 3:45 PM | Brief Back – Workgroup 2 | Dr. Steven Kaminsky Uniformed Services University of the Health Sciences | Room AB |
| 4:00 PM | Brief Back – Workgroup 3 | COL Karl Friedl Telemedicine and Advanced Technology Research Center | Room AB |
| 4:15 PM | Brief Back – Workgroup 4 | Dr. Erik Takhounts National Highway Traffic Safety Administration, U.S. Department of Transportation | Room AB |
| 4:30 PM | Summary – Specific Research Questions that Warrant Further Study | Col (sel) Marla De Jong DoD Blast Injury Research Program Coordinating Office | Room AB |
| 5:00 PM | Closing Remarks | Mr. Michael Leggieri DoD Blast Injury Research Program Coordinating Office | Room AB |

Thursday, May 14, 2009

| | | | |
|----------|------------------------------|--|--------|
| 7:30 AM | Continental Breakfast | | |
| 8:00 AM | Introduction | COL Karl Friedl , Panel Chair Telemedicine and Advanced Technology Research Center | Room C |
| 8:10 AM | Executive Session | Panel Members | Room C |
| 10:00 AM | Break | | |
| 10:20 AM | Executive Session | Panel Members | Room C |
| 12:00 PM | Lunch | | |
| 1:00 PM | Executive Session | Panel Members | Room C |
| 2:00 PM | Closing Remarks | Mr. Michael Leggieri DoD Blast Injury Research Program Coordinating Office | Room C |

C

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