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Mr. Chairman, Mr. Ranking Member, and Members of the Committee,
I appreciate the opportunity to appear today to discuss the Department of Veterans' Affairs (VA) efforts to address the progress in traumatic brain injury research, diagnosis, and treatment as it relates to academia-VA collaborations and ultimate clinical implementation.

Progress that has been made in understanding, diagnosing, and treating traumatic brain injury (TBI)
The annual incidence of TBI in the US is estimated at 1.5 million, and brain injury remains a major cause of long-term disability or death. Additionally, the yearly economic burden exceeds $60 billion, which does not include the social and emotional toll on patients, families, and the community. The understanding of TBI mechanisms has increased tremendously over the past 30 years, although this progress in scientific findings has not paralleled improvements in diagnosing and treatments for brain injured patients. Scientists have better tools to investigate cellular mechanisms of injury (i.e. what happens to the cells of the brain when they are injured) due to general advancements in genetics, molecular biology and biochemistry. Engineers use computers with much more computing power than previous generations. Working at the micro- and nano-levels, while unimaginable 20 years ago, is becoming commonplace at top research universities. Imaging techniques and processing capabilities has advanced quite rapidly, however, most hospitals do not have access to trained personnel, even IF they can afford the imaging equipment. These are just a few examples underlying improvements in TBI research and treatment.

Understanding TBI
The devastating events that surround a TBI are associated not only with the physical deformation of the brain, but also with secondary complications (such as inflammation, altered cellular signaling, and changes in gene expression – all of which affect cell function, organ function, and overall functional ability of the wounded). It is worthy to note that the high incidence of blast-related brain injuries in recent and ongoing US military operations has caused engineers and scientists to reconsider some of the animal models being used to study blast injury versus injury types that commonly occur in the US civilian population. Specifically, blast injuries occur at a much higher frequency than even motor vehicle accidents. The questions remain as to whether we can treat the basic mechanisms, learned over the past several decades, as the same in both populations. In addition, the competition among researchers— academic and military alike—in

developing these models has been overwhelming and very unlike the advent of animal models developed in the 1980's and 1990's for concussive and diffuse brain injury.

In both humans and animal models, complications that result from the primary insult (blast, head acceleration, or impact) can lead to cell death and progressive neurodegeneration, accompanied by prolonged or permanent loss of sensory, motor, and/or cognitive function. In order to understand the physical tolerance of neurons to traumatic insults, engineers and neuroscientists have attempted to reproduce the biomechanical environment during a traumatic event using cell, animal, and computer modeling. This approach allows one to begin to unravel the underlying injury mechanisms that lead to cell dysfunction and death as a function of input physics. To date, several cellular events have been identified that contribute to damage, such as cell membrane damage, imbalance of ions, abnormal release and deployment of normally controlled molecules, neurotransmitters, hormones, and enzymes. However, how these events relate to each other and how they can be targeted for therapeutic intervention are not well understood.

Diagnosing TBI

In October, 2007, the National Institute of NeurologicalDisorders and Stroke, with support from the Brain Injury Association of America, the Defense and Veterans Brain Injury Center, and the National Institute of Disability and Rehabilitation Research, convened a workshop to outline the steps needed to develop a reliable, efficient and valid classification system for TBI that could be used to link specific patterns of brain and neurovascular injury with appropriate therapeutic interventions. The primary system is the Glascow coma scale, as well as injury type, injury severity, pathoanatomy, and pathophysiology. It was agreed that compliant data sharing, uniform diagnostic criteria, and sophisticated modeling (prognostic modeling, informatics-based analyses, and more personalized diagnostics) are reasonable approaches to better stratifying patients. Success of the proposed changes, however, will require large center trials, integration of systems informatics to the neurotrauma field, and cooperation between academic and VA researchers.

On the advent of diagnostic techniques are biomarkers. Biomarkers are substances released in to the blood stream at high levels that may be associated with a particular type of lesion / region affected. The process is analogous to the blood tests given to help diagnosis heart attack severity.

Treating TBI – Current Clinical Therapies

Unfortunately, the current clinical treatments for TBI are very limited. Emergency care primarily addresses the acute physiological responses (e.g., controlling elevations in intracranial pressure and cerebral perfusion pressure) and long-term therapies are largely palliative measures. A large number of pharmacological therapies have gone to clinical trials for TBI; however, such treatments either focus on a single signaling cascade or the target spectrum has collateral detrimental effects systemically and have failed in clinical trials. As there are currently no FDA-approved therapeutic interventions for the treatment of TBI, developing efficacious treatment strategies remains an important research priority. TBI initiates an abundant number of highly complex molecular signaling pathways; thus, a multifaceted therapy is required to attenuate the degenerating injury environment. Other current clinical trials include therapies aimed at hindering the inflammatory response and provide neuroprotective effects, such as acute hypothermia (Adelson et al. 2005; Davies 2005), and early administration of erythropoietin

(Grasso et al. 2007), progesterone (Wright et al. 2005), and citicoline (Calatayud Maldonado et al. 1991). Moreover, clinical trials are also evaluating pharmaceutical therapies for post-TBI behavioral issues, such as depression, irritation, and aggression. Sertraline, a selective serotonin reuptake inhibitor, is one example of this treatment that addresses behavioral disorders that persist after a TBI (Fann et al. 2001; Zafonte et al. 2002). Each of these treatment modalities target specific events that occur after injury. Indeed, recent clinical advances using combination therapy, such as Highly Active Antiretroviral Therapy (HAART) to treat AIDS or in metastatic breast cancer, lend credence to this approach. Combination therapies for TBI is a relatively new approach only recently gaining acceptance. Their discovery may significantly shift clinical practice to target the underlying pathology rather than relying on surgical or symptomatic (i.e. intracranial pressure) management.

Given the complex and dynamic injury environment and interactions among secondary injury mechanisms, it is likely, if not required, that multiple agents will be needed to provide neuroprotection after TBI. Neuroprotection refers to the ability to SAVE cells. Repair and regeneration cannot provide their maximal benefit if the environment of the injured brain is not stabilized and receptive to regeneration. However, testing drug combinations is challenging given the combinatorial explosion of formulations. A traditional study may choose to test only two drugs, but such a strategy could easily miss more effective combinations and is essentially a fishing-expedition in a very tiny bucket. As an alternative, we have proposes a highly systematic, rigorous statistical approach to sample from a larger pool of literature-based candidates, whereby providing predictive capability for evaluation in vivo, streamlining the route to pre-clinical and clinical trials. The following categories of secondary damage have been selected, based on a wide literature search: 1) acute damage and excitotoxicity, 2) free radical damage and compromised energetics, and 3) inflammation. This is an example of a research approach that will operate out of the box and will hopefully be an example for others to follow on the path to translational discovery in neurotrauma. For example, novel combinations of FDA-approved drugs may be discovered, which could be fast-tracked into the clinic. These results will require non-biased dissemination, as well as a robust analysis platform.

Summarizing some of the top reasons why we don't have more options to treat TBI highlights the complexity faced and underlines the need for more cooperation and collaboration:
1) Heterogeneity of injuries between patients and within the brain means that one size will not fit all patients in terms of treatment or rehabilitation;
2) Injury mechanisms are poorly understood, due to the complexity of the brain microenvironment;
3) TBI changes over time (primary vs. secondary mechanisms; propensity to sudden onset neurodegenerative disease; complication with aging and other health issues), leaving the question as to when to intervene and how often;
4) Polytrauma, or trauma to many bodily systems (physiological and psychological), is commonplace, but not well studied, complicating research findings, diagnosis and treatment
5) The classification system (GCS and experimental) and the diagnosis systems are variable and crude;
6) No effective treatments exist clinically and we (all researchers and clinicians) need better avenues for collaboration and clinical translation;

7) It is unclear what are the right treatment target(s) to focus on? For example, is it neuroprotection vs. repair vs. regeneration vs. replacement?

Experience in collaborating with VA on TBI research and implementation of research findings
I have limited experience collaborating with the VA in Atlanta. The Atlanta VAMC Rehabilitation R&D Center of Excellence has recently undergone some restructuring and this will prompt reorganization and/or priorities shifting. The investigator and clinical staff have been extremely supportive and encouraging in navigating the system in order to find the right collaborators and passing along funding opportunities. I plan to submit to the fall cycle and in parallel seek a partial appointment at the VA. In addition to these plans, the Veterans' Innovation Center (VIC) (www.hinri.com) is an excellent example of local enthusiasm and timeliness. I commend Senator Isakson for his support of this initiative.

My impression is that the VA scientists are eager to collaborate with academic institutions and vis versa. There are several issues that hinder this process. The VA has a highly specialized and secured computer network. Virtual, secure data rooms may be a solution to the difficulty in communication and data sharing. There are different types of bureaucracy , but each is poorly understood by the other party.

Federal money for TBI research seems to be in silos, making cross-institutional and cross-agency collaboration difficult. It is my perception that TBI research finding within the Department of Defense is not shared with non-military institutions and vis versa, unless published in the public domain. The notion that upper-level review committees will match qualified grant applicants to appropriate researchers within military research institutions is nice in theory, but the most successful collaborations come from the ground up, not top-down. Conferences and other venues for data sharing need to include both civilian and military research sharing. Without this, the relationships will not develop and the collaboration success will move at a snail's pace.

Challenges of the future
Below are a summary of challenges that face researchers and clinicians, together with suggestions for improvement:
1) Cooperation between academic, medical, and military training facilities in terms of TBI awareness and care;
2) Better diagnostics – biomarkers – imaging – uniform registries across Level 1 Trauma Centers;
3) Platforms for deploying small, inexpensive diagnostic "kits" to smaller hospitals and portable/ temporary medical units – i.e. no large equipment, easy steps, stable at a range of environment conditions;
4) Many more and uniformed programs to filter research findings in an unbiased manner. In other words, beyond open access journals, the mere volume of scientific papers published limits investigators. Government databases with secure access that are professional designed to maximize dissemination and interpretation of published work;
5) Programs that encourage and fund pre-clinical experiments with large numbers of interventions (pharmaceuticals, biologics) and in combinations that provide widespread screening, rather that narrow investigations that don't take into consideration the complexity of TBI;

6) Cross-agency collaborative funding mechanisms designed for data sharing, uniform financial and administrative responsibility, and shared resources;
7) Proactive involvement of informatics and information science to consolidate and analyze large and diverse data sets from basic lab studies to pre-clinical studies to clinical trials. The advent of traumanomics—to follow along with the "–omic" nomenclature adopted in the 21st Century—is relatively new, but yet few investigators understand or appreciate the necessity to use unbiased statistical and multilevel modeling. Freely providing data to such "number crunching" efforts goes against the culture of publications;
8) Open dissemination of findings, including unpublished data and protocols;
9) Open dialogue among educators, policy makers, clinical leadership, and research directors.

In closing, the fields of neurotrauma and trauma medicine are at a very exciting crossroads. We have learned so much about injury mechanisms and are beginning to appreciate the complexity and wide variety of pathologies associated with TBI. Successful implementation of the findings is possible, providing cooperation is focused on the patient or warfighter / veteran. I thank the committee for providing me the opportunity to share my experience and recommendations on TBI with respect to veteran's healthcare.