DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420

June 17, 2008

OFFICE OF RESEARCH AND DEVELOPMENT
PROGRAM ANNOUNCEMENT
TRAUMATIC BRAIN INJURY

1. **Purpose**

The Department of Veterans Affairs (VA) Office of Research and Development (ORD) offers this program announcement to stimulate research in the area of Traumatic Brain Injury (TBI). Due to the ongoing conflicts in Afghanistan and Iraq, TBI accounts for a significant portion of combat causalities. On April 30, 2008 – May 2, 2008, ORD sponsored a State of The Art (SOTA) conference on TBI, with panel members representing academia, VA, the Department of Defense, and the National Institutes of Health. This conference highlighted the state of knowledge in TBI research and also identified areas of scientific priority. This program announcement is in part informed by the results of this conference. Scientifically meritorious proposals addressing issues concerning TBI are sought. Proposals may be submitted to VA's Biomedical Laboratory Research Service (BLR&D), Clinical Science Research and Development Service (CSR&D), Health Services Research and Development Service (HSR&D), or Rehabilitation Research and Development Service (RR&D).

2. **Background**

A majority of combat injuries in Afghanistan and Iraq result from high pressure waves, shrapnel, and acceleration / deceleration injury from explosive devices. Although Kevlar helmets and advances in body armor have saved the lives of many soldiers and protect against penetrating injury, they do not fully protect against blasts and impacts especially to the head and face. In order to advance treatment and rehabilitation following TBI, fundamental information about the post-acute and long-term physiological and psychological consequences are essential. Blast injuries often result in multiple traumas, including injuries to internal organs, limb loss, sensory-motor loss, and neuro-psychological disorders. The term "polytrauma" has been coined to describe the co-occurring injuries.

Traumatic Brain Injury:

The frontal and temporal lobes of the brain are often damaged in traumatic brain injury. These areas of the brain control intellectual abilities, executive functions, personality, behavior, and emotion. Concussive or mild TBI (mTBI) is the most common form of combat-related injury, and can be caused by acceleration / deceleration, impact, and / or blast trauma. Mild TBI can occur even in those not directly hit by a blast, without obvious external injuries, and without loss of consciousness. Problems with memory, lack of concentration, increased anxiety and irritability are common hallmarks of mTBI. Recently studies on subjects with mTBI have demonstrated microstructural lesions in the white matter, also known as diffuse axonal injury (Niogi et al., 2008; Rutgers et al., 2008; Wilde et al., 2008). Although psychological complications such as post-traumatic stress and depression may account for some of the

symptoms of mTBI, the full extent of damage from mTBI as determined by imaging and other approaches needs further evaluation.

In addition to mild TBI, service men and women close to blasts experience severe injuries. Those with moderate to severe TBI can have persistent difficulties in executive function, sensory difficulties, and emotional disturbances. Common symptoms include headaches, repeated vomiting or nausea, seizures, sleep disturbances, slurred speech, balance problems, visual disturbance, weakness, numbness, and loss of coordination. Unlike mild TBI, these problems and others can persist long-term or result in permanent difficulties with memory, reasoning, emotion, and expression making it difficult to hold steady employment or regain pre-injury quality of life.

3. **Sample Research Issues**

Research considered responsive to this announcement and of interest to the Research Services within ORD, is described below.

Research leading to the development of new, effective treatments is particularly of interest. For clinical studies, proposed patient populations should be carefully described, including access to appropriate cases and feasibility of recruiting and enrolling. Proposals should carefully consider other ongoing funded programs in these veteran populations to develop novel approaches for prevention and treatment.

Topics responsive to this announcement include TBI and associated co-morbid conditions including:

- cognitive dysfunction
- mood and anxiety disorders (including depression, PTSD, acute stress disorder, etc)
- vision and/or hearing deficits related to blast injury
- post-traumatic epilepsy
- chronic pain
- substance abuse
- suicidality
- sleep disturbances

Proposals submitted to **BLR&D** should focus on the etiology, pathogenesis, and/or genetics of Traumatic Brain Injuries. Proposals employing novel concepts or approaches are especially welcome. Areas of particular programmatic interest include, but are not limited to:

1. Development of innovative animal and in vitro models for blast-force-associated mild to severe brain injury.
2. Development and validation of efficient diagnostic criteria for detecting mild TBI, including diagnostic imaging technology (DTI, fMRI, MRI, PET) and development of novel neuropsychological/ behavioral instruments.

3. Development of innovative regenerative medicine approaches to treat TBI (i.e., neural repair, cell therapy, etc.).
4. Identification of the cellular/molecular and pathological changes resulting from TBI and the mechanisms underlying these changes (i.e., edema and vasospasm).
5. Understanding the relationships between the neurobiology and neuropsychological/behavioral effects of sub-acute and chronic TBI.
6. Innovative treatment approaches to late or long-term consequences of TBI, such as post-traumatic epilepsy and neurodegenerative disease (including primary prevention strategies).
7. Identification of factors influencing metabolic and body composition changes after TBI, such as pituitary dysfunction, and identification of potential therapeutic targets.
8. Comparisons of pathophysiology and/or treatment of TBI that results from blast injury with that which results from acceleration / deceleration injury.

Proposals submitted to **CSR&D** should focus on the etiology, pathogenesis, and/or genetics of traumatic brain injury. Proposals employing novel concepts or approaches are especially welcome. Areas of specific CSR&D interest include, but are not limited to:

9. Development and validation of efficient diagnostic criteria and treatment milestones for mild TBI, including diagnostic imaging technology (DTI, fMRI, MRI, PET) and development of novel neuropsychological instruments.
10. Innovative regenerative medicine approaches to treat TBI (i.e., neural repair, cell therapy, etc.).
11. Identification of the cellular/molecular and pathological changes resulting from TBI and the mechanisms underlying these changes (i.e., edema and vasospasm).
12. Understanding the relationships between the neurobiology and neuropsychology of TBI including co-morbid diagnoses such as PTSD.
13. Innovative treatment approaches to late or long-term consequences of TBI, such as post-traumatic epilepsy and neurodegenerative disease (including primary prevention strategies).
14. Identification of factors influencing metabolic and body composition changes after TBI, such as pituitary dysfunction, and development of novel interventions.
15. Comparisons of pathophysiology and/or treatment of TBI that results from blast injury with that which results from acceleration / deceleration injury.

RR&D

Appropriate topics for investigation under this RFA would include but are not limited to:

A. Post-acute TBI

16. Development of innovative, animal and *in vitro* models predictive of human response for blast-force-associated mild to severe brain injury.
17. Development of efficient clinical diagnostic criteria and treatment milestones for detecting mild TBI, while distinguishing it from psychological co-morbidities (i.e. depression and PTSD).
18. Validation and refinement of diagnostic imaging technology (DTI, fMRI, MRI, PET).
19. Development of novel neuropsychological instruments to aid in the diagnosis of mTBI.
20. Innovative regenerative medicine approaches to treat TBI and visual, auditory and/or vestibular deficits (*i.e.*, stimulating endogenous neural repair, use of biomaterials and/or cell therapy, *etc.*).
21. Identification of the cellular/molecular and pathological changes resulting from TBI and the mechanisms underlying these changes (*i.e.*, edema and vasospasm).
22. Understanding the relationships between the neurobiology and neuropsychology of sub-acute and chronic TBI.
23. Identification and development of novel therapies to treat sensory deficits associated with TBI and blast injuries, (i.e. visual, auditory and/or vestibular deficits and pain), including delayed onset.

B. Chronic TBI

24. Innovative approaches to late or long-term consequences of TBI, such as post-traumatic epilepsy and neurodegenerative disease (including primary prevention strategies).
25. Development of rehabilitative engineering platforms to treat visual, auditory and/or vestibular deficits.
26. Impact of rehabilitation strategies on neural plasticity following TBI, using imaging, neurobiological, and cognitive approaches.
27. Identification of factors influencing metabolic and body composition changes after TBI, such as pituitary dysfunction and alterations in mobility and lifestyle and development of interventions, and other co-morbid medical conditions.
28. Examination of the continuity of care while transitioning from Department of Defense Military Treatment Facilities to the Polytrauma Centers and from the Polytrauma Centers into VA's inpatient or outpatient health care system.
29. Comparisons of pathophysiology and/or treatment of TBI that results from blast injury with that which results from acceleration / deceleration injury.

C. Rehabilitation and Community-reintegration

30. Innovative approaches to short- and long-term consequences of TBI that affect relationships, employment and ultimately reintegration, examples include cognitive deficits, mood impairment, self-awareness, and planning.
31. Establish outcomes and effectiveness of clinical and rehabilitation interventions for TBI and its sequelae.
32. Development and comparison of novel intervention strategies for care-giving and family coping, such as education, support groups, and therapy.
33. Examination of patient recruitment and attrition in service use that are potential barriers to accessing the continuum of available care.
34. Treatment trials to enhance cognition and attention and to treat emotional, behavioral, and psychomotor conditions related to TBI, including physical and emotional intimacy between partners.
35. Identification of issues related to community reintegration and intervention strategies to address them.
36. Vocational Rehabilitation training for persons mild to severe TBI.

HSR&D

Areas of particular programmatic interest to **Health Services Research and Development Service** include:

A. Issues related to the operational definition of mild TBI, such as:

37. Development and testing of current and/or new definitions, taxonomies or symptom clusters to describe or classify the presence of mild TBI, including clinical criteria that delineate the relationships among blast injury, psychiatric disorders, particularly PTSD, and functional capacity.
38. Development and testing of definitions, taxonomies or symptom clusters that examine the similarity and dissimilarity among blast, closed, penetrating, or blunt trauma associated TBI.
39. Examination of the interrelationships between objective signs and subjective measures of postconcussive symptoms and co morbid conditions including PTSD.

B. Issues related to the development and evaluation of TBI screening instruments, such as:

40. Evaluation of the psychometric properties of the current VA TBI screen (including but not limited to its reliability, validity, sensitivity, and specificity).
41. Identification of approaches to improve the TBI screening protocol within VA, including methods for evaluating alternative approaches. These approaches should take into consideration the feasibility of implementation in VA settings including primary care as well as polytrauma and tertiary care settings.

42. Identification of methods to improve screening for TBI, which should take into consideration the existence of co-occurring psychiatric conditions, including but not limited to PTSD.
43. Identification of efficient and psychometrically sound methods of screening for sensorimotor sequelae of TBI, including but not limited to, visual dysfunction, auditory dysfunction, vestibular and sleep disturbance.

C. Issues related to the development and evaluation of instruments that measure the presence of, recovery from, and longitudinal outcome of TBI, particularly mild TBI, such as:

44. Development and evaluation of measures to examine short- and long-term symptomatic consequences of TBI that affect recovery, response to treatment, functioning, reintegration and quality of life, including physiologic, orthopedic, neurologic, psychiatric, and neuropsychological factors such as pain, cognition, mood, self-awareness, and executive/planning capabilities.
45. Development and examination of measures to assess short- and long-term factors that impact recovery, response to treatment, functioning, and reintegration, including interpersonal, social, and economic domains.
46. Examination of the prevalence and burden of co-morbid conditions in individuals with mild TBI, including but not limited to depression, PTSD, pain, sleep, epilepsy/ non-epileptic seizures, substance abuse, cognitive dysfunction, and suicide.
47. Identification of patient preferences that impact recovery, response to treatment, functioning, reintegration, and quality of life.

D. Issues related to needs and barriers assessment of mild, moderate, and severe TBI, such as:

48. Identification of service use patterns and barriers to accessing the continuum of available care.
49. Impact of TBI on the family unit (including spouses, parents, children, siblings, and significant others).
50. Challenges in accessing and resources for community reintegration.
51. Assessment of risk and resilience factors for mild TBI.

E. Issues related to treatment of TBI, particularly mild TBI, such as:

52. Development, examination, and comparison of models of service delivery and care management that promote optimal recovery, rehabilitation, and reintegration.
53. Development, examination, and comparison of interventions to enhance cognition and attention, and treat emotional, behavioral, and psychomotor conditions related to TBI.

54. Development, examination, and comparison of decision-making, communication and intervention strategies for caregiving and family coping, such as education, telehealth, support groups, and therapy.
55. Identification of factors and development of models that predict responsiveness to rehabilitative/therapeutic interventions.
56. Assessment of treatment outcomes for TBI and co-occurring conditions, including enduring symptoms, functional status (especially vocational status) and disabilities.
57. Sustainability and cost effectiveness of clinical and rehabilitation interventions for TBI and its sequelae.

F. Issues related to study design and methods, such as:

58. Examination of methods for studying the effect of combat-related TBI on health outcomes and health-related quality of life. This includes TBI that is not diagnosed immediately after the traumatic exposure and that occurs in the context of other conditions, including psychiatric disorders, pain, sensory, cognitive and motor dysfunction.
59. Development and examination of research methods for studying the effect of interventions on health outcomes and functioning among veterans with combat-related TBI. This may include research designs with a small sample.
60. Identification of methods to model the effects of co-occurring conditions, such as depression, anxiety, PTSD, headache, and sleep complaints.
61. Identification of psychometrically sound and clinically efficient methods and measures to evaluate longitudinally various co-morbid conditions of patients with TBI.

5. **Eligibility**

Eligibility to submit proposals will follow the same rules established by the individual ORD service for submission of investigator-initiated proposals.

6. **Application Preparation and Submission**

Proposals can be electronically submitted for review by any of the four ORD Services. The same proposal cannot be sent to more than one ORD Service at the same time. Please follow the submission and funding guidelines of the ORD Service to which the proposal will be submitted. Visit the following URL for the latest instructions on preparing and submitting electronic applications: http://vaww.research.va.gov/funding/electronic-submission.cfm.

Specific RFAs for electronic submission are located at:
http://vaww.research.va.gov/funding/rfa.cfm

7. **Due Date**

Research proposals may be submitted through Fiscal Year 2012 for any of the regular merit review receipt dates established by the relevant Service as outlined on the ORD web site at http://www.research.va.gov/funding/process/submission-calendar.cfm.

8. **References**

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9. **Review**

Established deadlines and review procedures for each ORD service apply. Proposals will be evaluated on the basis of scientific quality, significance and innovation of the research question(s), rigor of the methodological approach, and feasibility.

10. **Inquiries**

For further information, please direct all questions regarding this program announcement including questions about areas of research investigation, eligibility, application preparation funding, and review to the individuals identified below for each ORD Service:

Biomedical Laboratory R&D: Joseph Webster, PhD at (202) 254-0273 or joseph.webster@va.gov.

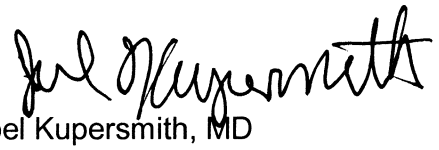
Clinical Science R&D: Joseph Webster, PhD at (202) 254-0273 or joseph.webster@va.gov.

Health Services R&D, Martha Bryan, EdD, 202-254-0251 or martha.bryan@va.gov.

Rehabilitation R&D: Audrey Kalehua, PhD. at 202 -254-0129 or audrey.kalehua@va.gov.

11. **Expiration Date**

This solicitation will be updated or expire by the last day of September 2012.



Joel Kupersmith, MD
Chief of Research and Development Officer

OFFICE OF RESEARCH AND DEVELOPMENT
PROGRAM ANNOUNCEMENT
TRAUMATIC BRAIN INJURY

1. **REASON FOR ISSUE:** This Office of Research and Development (ORD) announcement encourages innovative Traumatic Brain Injury research for veterans.

2. **SUMMARY OF MAJOR CHANGES:** Focuses interest in Traumatic Brain Injury.

3. **RESPONSIBLE OFFICE:** The Office of Research and Development (12) is responsible for the contents of this VHA announcement. Questions may be referred to Martha Bryan, EdD at 202-254-0251 or martha.bryan@va.gov for HSR&D; to Audrey Kalehua, PhD. at 202 -254-0129 or audrey.kalehua@va.gov for RR&D; to Joseph Webster, PhD at (202) 254-0273 or joseph.webster@va.gov for BLR&D and CSR&D.

4. **RECISSION:** ORD Program Announcement on Combat Casualty Neurotrauma (September 3, 2005).