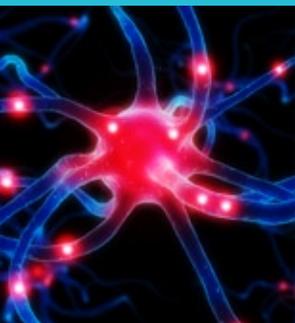


Psychological Health/ Traumatic Brain Injury Research Program



Congressionally Directed Medical Research Programs



HISTORY In 1992, the Office of the Congressionally Directed Medical Research Programs (CDMRP) was born from a powerful grassroots effort led by the breast cancer advocacy community that convinced Congress to appropriate funds for breast cancer research. This enabled a unique partnership among the public, Congress, and the military. Created within the U.S. Army Medical Research and Materiel Command (USAMRMC) to manage these critical funds, the CDMRP has grown to encompass multiple targeted programs and has received \$5.4 billion in appropriations from its inception through fiscal year 2009 (FY09). Funds for the CDMRP are added to the Department of Defense (DOD) budget, where support for individual programs such as the Psychological Health and Traumatic Brain Injury (PH/TBI) Research Program is allocated via specific guidance from Congress.

Two-Tier Proposal Review Process

The CDMRP uses a two-tier review process for proposal evaluation, with both steps involving dynamic interaction between scientists, clinicians, and disease survivors. The first tier of evaluation is a scientific peer review of proposals weighed against established criteria for determining scientific merit. The second tier, programmatic review, compares submissions and recommends proposals for funding based on scientific merit and overall program goals. The first tier of review involves both scientist and consumer reviewers. These consumers (individuals suffering from TBI and/or PH challenges, including family members) provide a broad perspective on issues critical to addressing PH and TBI among warfighters.



Psychological Health and Traumatic Brain Injury Research Program

VISION:

Prevent, mitigate, and treat the effects of traumatic stress and TBI on function, wellness, and overall quality of life for service members as well as their caregivers and families.

MISSION:

Establish, fund, and integrate both individual and multi-agency research efforts that will lead to improved prevention, detection, and treatment of PH/TBI.

The PH/TBI Research Program was funded in the FY07 war supplement and administered by the USAMRMC office, the CDMRP. This program was established in response to the U.S. Troop Readiness, Veterans' Care, Katrina Recovery, and Iraq Accountability Appropriations Act, Public Law 110-28, which provided \$150 million (M) for research on post-traumatic stress disorder (PTSD) and \$150M for research on TBI. An additional \$1M was appropriated to PTSD research per Conference Committee Report Number 109-676. A key priority of the PH/TBI Research Program is to complement ongoing DOD efforts to ensure the health and readiness of our military forces. This \$301M congressional special interest supplemental funding was aimed at promoting a better standard of care for PH (including PTSD) and TBI in the areas of prevention, detection, diagnosis, treatment, and rehabilitation. This includes research to benefit service members, their family members, veterans, and other beneficiaries of the Military Health System. Of the \$301M, \$45M was assigned to the Defense Centers of Excellence (DCoE) for Psychological Health and Traumatic Brain Injury for investment; information about the DCoE can be found at <http://www.dcoe.health.mil>.

A stakeholders meeting was held in June 2007 to assess the state of the science for the purpose of identifying gaps in the areas of PTSD and TBI research. Participants included representatives from the four services, the Office of the Secretary of Defense for Health Affairs (OSD[HA]), the Uniformed Services University of the Health Sciences (USUHS), the U.S. Department of Veterans Affairs (VA), the National Institutes of Health (NIH), private industry, and academia. Six PTSD and five TBI research gaps were identified by these stakeholders.

A vision setting meeting followed on June 13, 2007. The purpose of the vision setting meeting was to prioritize the research gaps identified by the stakeholders, establish program goals and objectives, and develop an investment strategy for the \$277.3M assigned to the CDMRP for management. Vision setting was conducted by a Joint Program Integration Panel, which consisted of representatives from the four services, the OSD(HA), USUHS, VA, and NIH.

PH/TBI Research Program

...Filling Important Gaps

PTSD Research Gaps	TBI Research Gaps
Treatment and Intervention	Treatment and Clinical Management
Prevention	Neuroprotection and Repair Strategy
Measures in Screening, Detection, and Diagnosis	Rehabilitation/Reintegration Strategies
Epidemiological Studies	Field Epidemiology
Families/Caregivers Projects	Physics of Blast as It Relates to Brain Injury

In FY07, program announcements for 4 intramural and 12 extramural award mechanisms were released. These mechanisms challenged the scientific community to design innovative research that will foster new directions, fill research gaps, and bring new investigators into the fields of PH- and TBI-focused research. Of the 2,110 proposals received, 201 were funded. The FY07 investment portfolio for the PH/TBI Research Program is illustrated in Figures 1-7. These data are categorized by Gap Areas (Figures 1 and 4), Clinical Categories (Figures 2 and 5), and Topic Areas (Figures 3, 6, and 7)

Figure 1. PH-Funded Projects by Gap Area

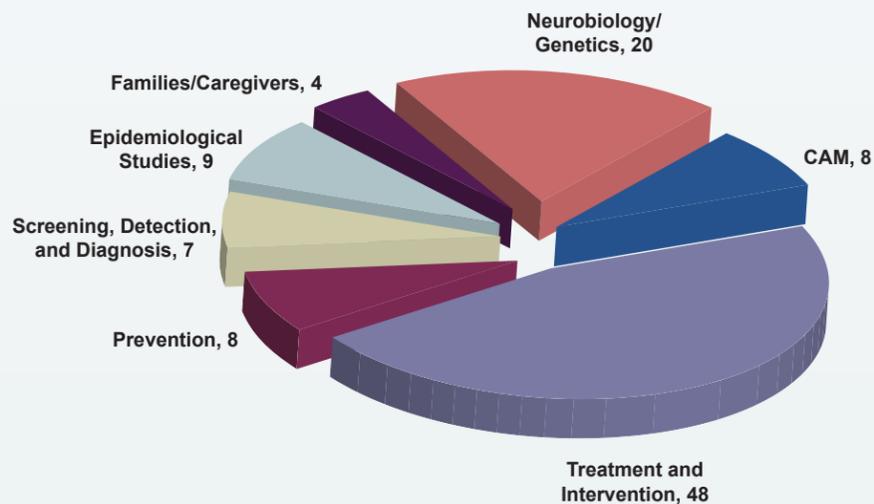


Figure 2. PH Clinical Categories

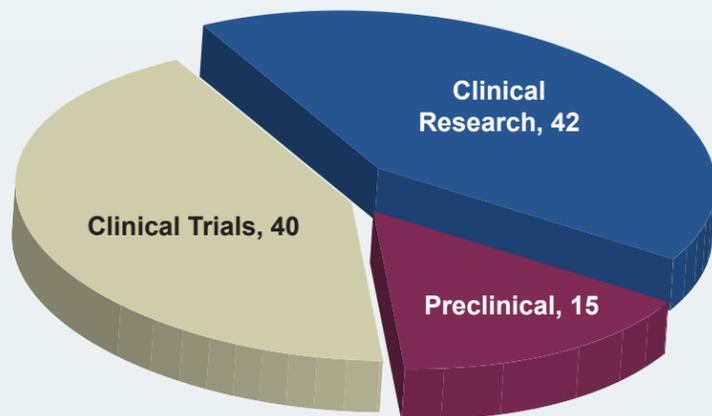


Figure 3. Delineation of PH Clinical Research Topic Areas

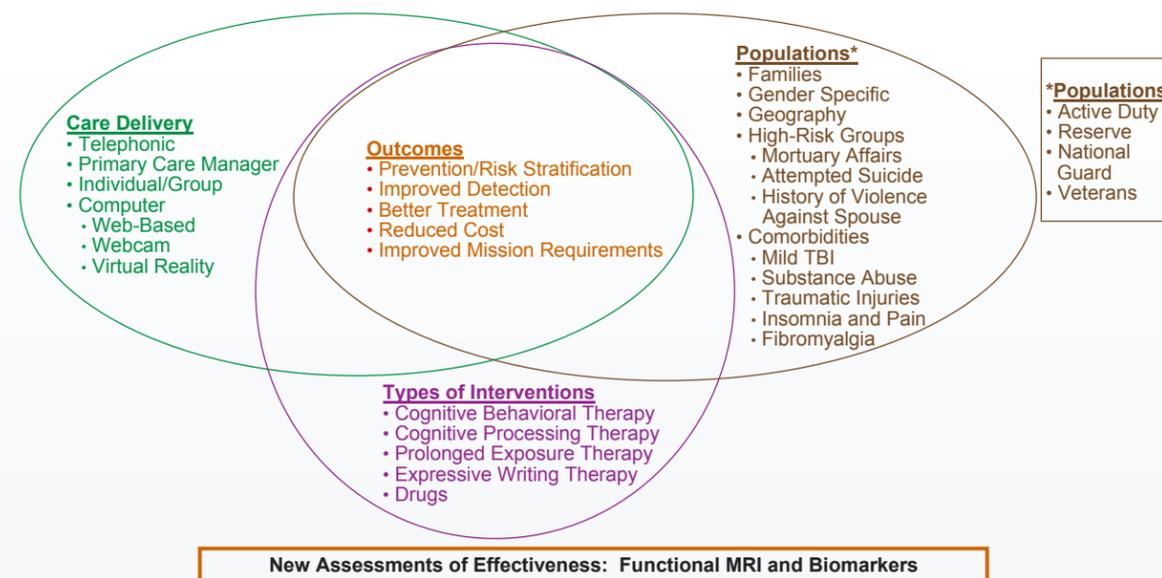


Figure 4. TBI-Funded Projects by Gap Area

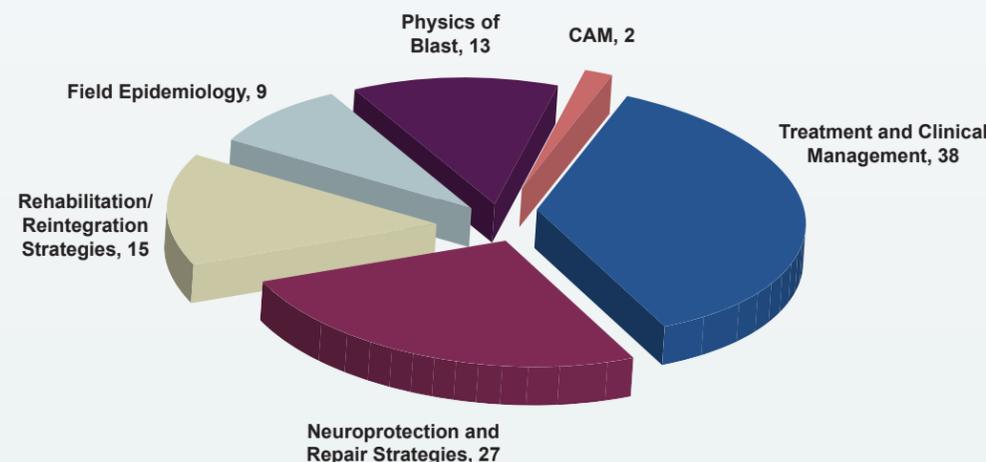


Figure 5. TBI Clinical Categories

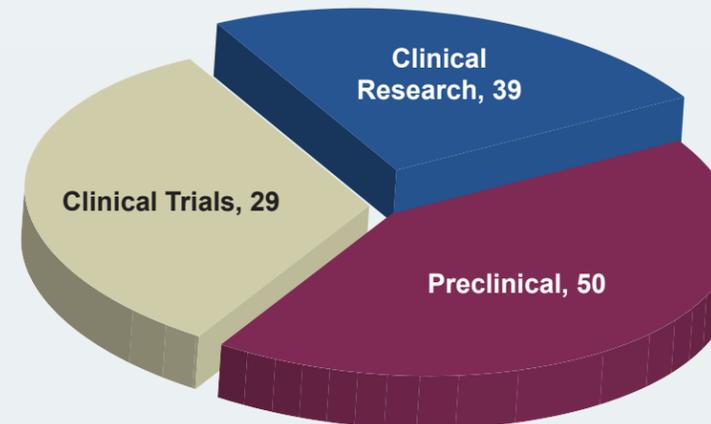
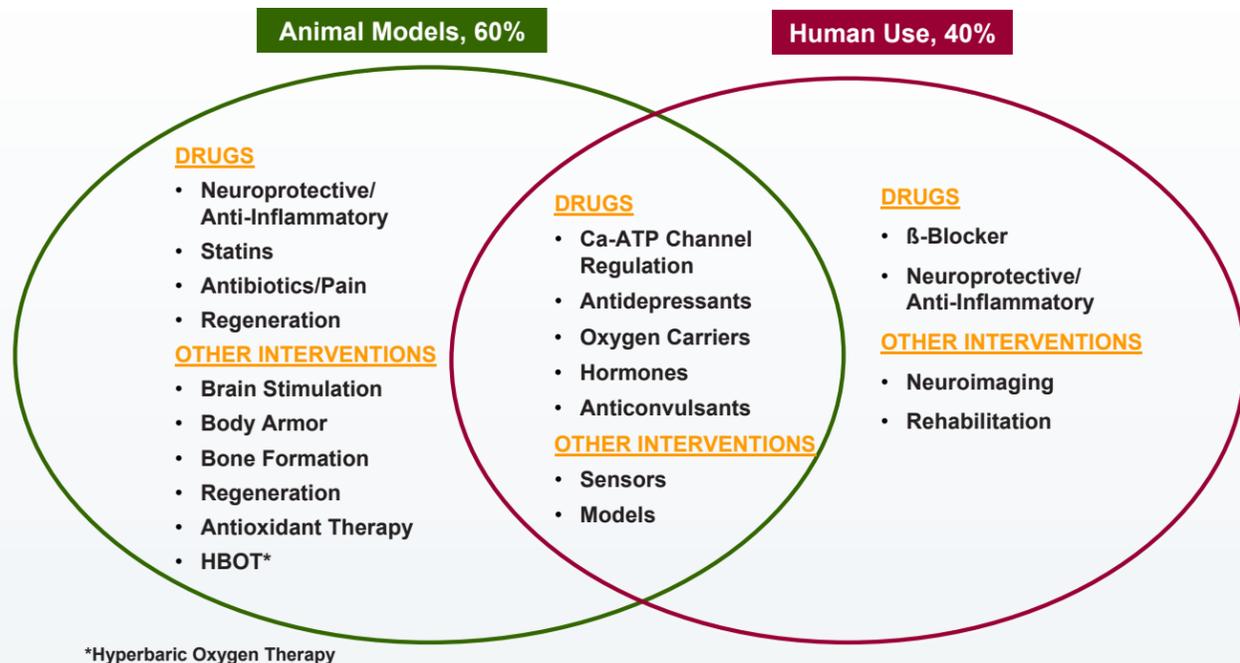


Figure 6. Delineation of TBI Portfolio by Broad Topic Areas: Interventions



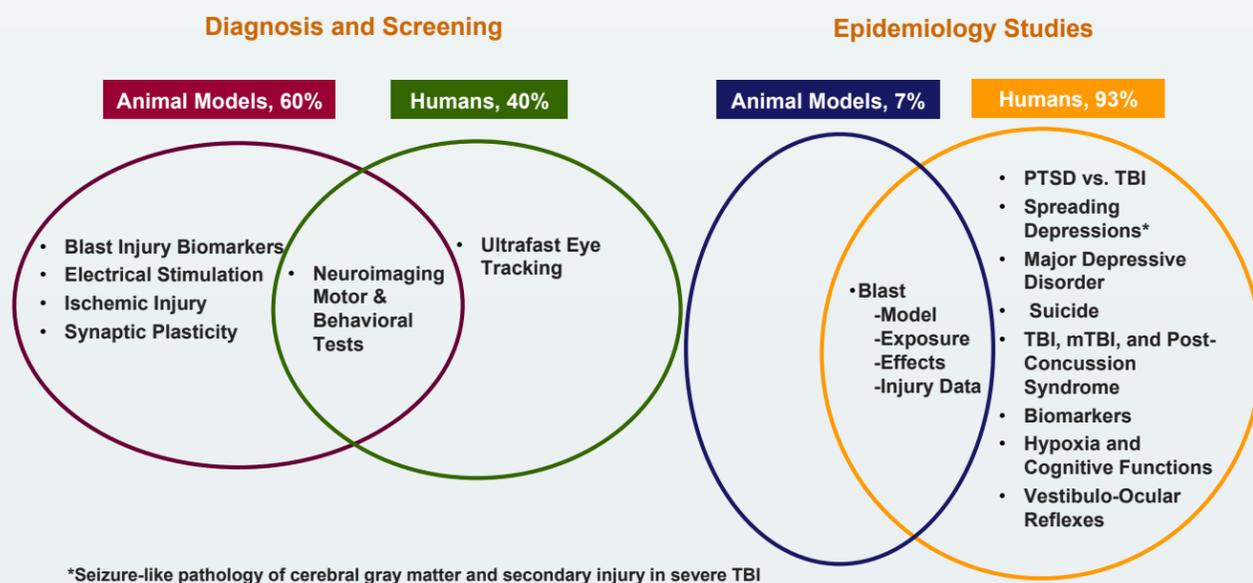
Filling Important Gaps Through Unique Partnerships

The PH/TBI Research Program recognizes the contributions of many individuals whose commitment and innovative approaches to research have made a large impact in the fields of PH and TBI. Partners of the PH/TBI Research Program include Congress, DOD, the VA, the U.S. Department of Health and Human Services, peer review panel members, consumer advocates, and the scientific community, all of whom joined efforts to address the needs of those with PH and TBI challenges.

Peer Review Panel Members

PH/TBI peer review panel members represent a renowned group of research scientists, clinicians, and consumer advocates who provide expert advice on the scientific and technical merit of proposals. Scientific reviewers are selected for their subject matter expertise and experience with scientific peer review. More than 380 scientists and 40 consumer advocates have served on peer review panels for the PH/TBI Research Program.

Figure 7. Delineation of TBI Portfolio by Broad Topic Areas: Diagnosis/Screening and Epidemiology Studies



“I was proud to participate as a reviewer for the CDMRP FY07 Psychological Health/Traumatic Brain Injury Research Program. The dedication, efficiency, and professionalism of the CDMRP staff were impressive. The quality of applications was excellent, and I am confident that outstanding work will be performed because of this important program.”

Neil Grunberg, Ph.D.
Uniformed Services University of the Health Sciences



“Astute and unbiased peer review is critical to the success of any program designed to support high-quality scientific research. The CDMRP continues to work assiduously to evaluate and improve their peer review process. It is a challenge and a privilege to participate in the peer review process for the Psychological Health/Traumatic Brain Injury Research Program of the CDMRP.”

Douglas Dewitt, M.D.
The University of Texas Medical Branch

Integration Panel Members

Serving on the Integration Panel are innovative, prominent members of the PH and TBI community. The Integration Panel recommends a broad portfolio of proposals for funding that reflects the investment strategy for that particular program cycle.

FY09 PH/TBI Research Program Integration Panel

BG Loree Sutton (Chair)
DCoE for PH and TBI

Dr. Sonja V. Batten
(Primary Alternate Chair)
DCoE for PH and TBI

CAPT (S) Russell Shilling
(Secondary Co-Alternate Chair)
DCoE for PH and TBI

Mr. Michael Leggieri
(Secondary Co-Alternate Chair)
USAMRMC

COL Carl Castro
USAMRMC

Dr. Kenneth Curley
USAMRMC

Dr. Terri Gleason
Department of Veterans Affairs

Col Richard Griffith
U.S. Air Force, Medical Modernization

Ms. Katherine Helmick
DCoE for PH and TBI

Dr. Ramona Hicks
National Institute of Neurological
Disorders and Stroke

Dr. Steven Kaminsky
Uniformed Services University of the
Health Sciences

COL Geoffrey Ling
Defense Advanced Research Projects
Agency

CAPT Mark Lyles
U.S. Navy Bureau of Medicine and
Surgery

Dr. E. Jane McCarthy
Montgomery County Veterans
Commission

COL Richard Ricciardi
DCoE for PH and TBI

LCDR Alfredo Sancho
DCoE for PH and TBI

CAPT Edward Simmer
DCoE for PH and TBI

Dr. Farris Tuma
National Institute of Mental Health

Consumers

Consumer reviewers are nominated by an advocacy or support organization, and they are selected on the basis of their commitment to advocacy, interest in science, and ability to represent the collective views of the PH and TBI consumer community. Firsthand experience with PH/TBI provides each consumer advocate with a unique perspective that complements the expertise of the scientists and clinicians on the peer review and integration panels. This perspective helps scientists understand the human side of how the research will impact the community, encouraging funding recommendations that reflect the concerns and needs of patients and their families.

“Being a part of this was a huge honor. I had the opportunity to see and speak with so many great minds—all of whom had come together with one common goal, to support the Soldiers who had been injured as they fought for their country. I am grateful to have had this opportunity.”

Richard Flores
FY07 Psychological Health Consumer Peer Review Panel Member



“I felt a great responsibility and honor to have been a part of this program. I think we owe it to all our returning Soldiers to find the best medical treatment available for TBI and PTSD, not only to help the returning Soldiers, but to help their families as well.”

Penny Flores
FY07 Psychological Health Consumer Peer Review Panel Member



The PH/TBI Research Program Fills Important Gaps

...By Implementing a Multidisciplinary Approach to Address Military-Relevant PH and TBI

Three multi-institutional consortia were funded in FY07 to address military-relevant PH and TBI research gaps. Information on these innovative projects follows.

PTSD/TBI Clinical Consortium

Murray Stein, University of California, San Diego

The overarching goal of establishing the PTSD/TBI Clinical Consortium is to combine the efforts of the nation's leading investigators to bring to market novel treatments or interventions that will ultimately decrease the impact of military-relevant PTSD and TBI and improve the function, wellness, and overall quality of life for service members and their families and caregivers, and the American public. Dr. Murray Stein is leading the consortium, also known as INTRuST (Injury & Traumatic Stress Consortium) that comprises a Coordinating Center at the University of California, San Diego, and 10 clinical sites, each of which is participating in clinical trials in PTSD and/or TBI. The 10 Principal Investigators and clinical sites are Dr. Howard Eisenberg (University of Maryland), Dr. David Benedek (USUHS), Dr. Ross Zafonte (Spaulding Rehabilitation Hospital), Dr. Thomas McAllister (Dartmouth College), Dr. Nancy

Temkin (University of Washington), Dr. Lori Shutter (University of Cincinnati), Dr. Gerald Grant (Duke University), Dr. Raul Coimbra (University of California, San Diego), Dr. Mark George (South Carolina Research Authority/Medical University of South Carolina), and Dr. Gregory Gahm (National Center for Telehealth and Technology (T2) and T2 Directorate of the Defense Centers of Excellence for PH and TBI/Madigan Army Medical Center).

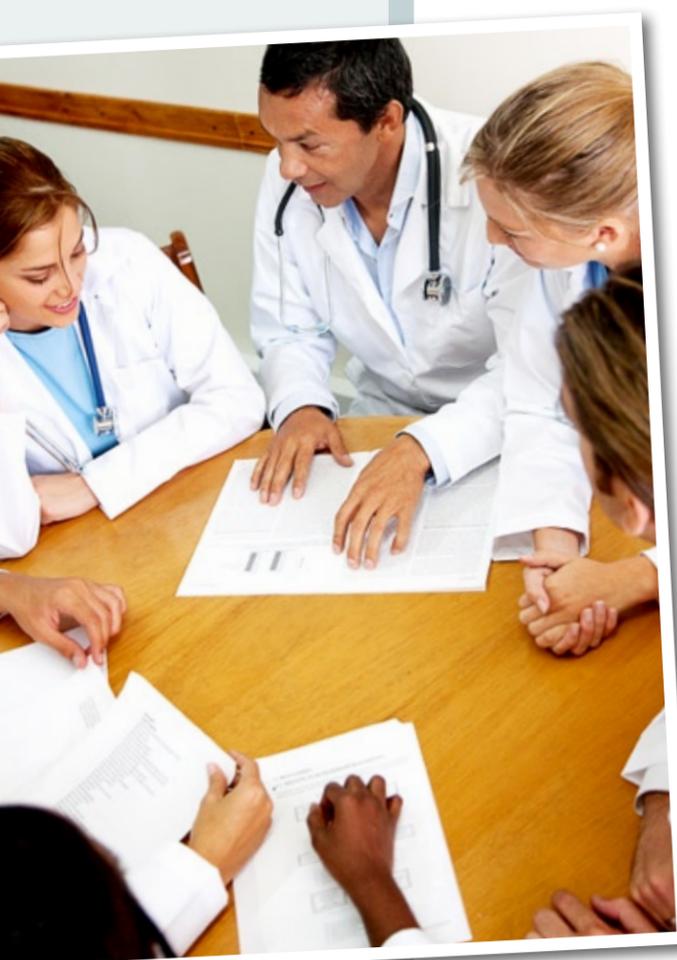
“The Clinical Consortium is focused on finding and validating new treatments for military personnel and civilians who suffer from the neurological, psychological, and cognitive after-effects of traumatic stress and injury. We recognize that existing treatments for these conditions—which include PTSD and mTBI [mild TBI]—are inadequate, and it is our mission to bring novel and better treatments to the patients who need them.”

“We will be bringing together psychologists, psychiatrists, neurologists, neurosurgeons and trauma surgeons, and rehabilitation specialists to design and conduct studies that help us answer questions about what really happens with people who suffer mild head injuries such as concussions.”

“This will help us better understand how we should be following up and providing appropriate care. Moreover, both PTSD and TBI frequently occur in the same patient after an injury. The Clinical Consortium will be devoting special efforts to understand and develop treatments for the overlap between these two conditions.”

Murray Stein, M.D.

University of California, San Diego



PH Multidisciplinary Research Consortium

Alan Peterson, University of Texas Health Science Center at San Antonio

The PH Multidisciplinary Research Consortium, called STRONG STAR (South Texas Research Organizational Network Guiding Studies on Trauma and Resilience), is dedicated to the development and evaluation of the most effective early interventions for the detection, prevention, and treatment for combat-related PTSD in active-duty military and recently discharged veterans. The STRONG STAR Consortium will evaluate the impact of comorbid conditions (i.e., burns, chronic pain, alcohol abuse, amputation, TBI, and insomnia) on the etiology, prevention, and treatment of PTSD. Treatment interventions, epidemiology, neurobiology, imaging, and genomic studies will be conducted to better understand PTSD risk, resilience, and prevention and to stimulate novel approaches to treatment development, selection, and response. In addition, the consortium will train multidisciplinary scientists to pursue careers devoted to the detection, prevention, and treatment of combat-related PTSD. The STRONG STAR team is under the direction of Dr. Alan Peterson and includes nine partnering Principal Investigators: Dr. Edna Foa (University of Pennsylvania School of Medicine), Dr. Robert Gatchel (University of Texas at Arlington), Dr. David Riggs (USUHS), Drs. Brett Litz and Patricia Resick (National Center for PTSD/VA Boston Healthcare System), and Drs. John Roache, Randy Strong, Peter Fox, and Michael Escamilla (University of Texas Health Science Center at San Antonio).

“Recent research on U.S. service members returning from Iraq and Afghanistan highlights the significant risk of military deployment on the psychological health of these combat veterans. The development and evaluation of evidence-based interventions for the prevention and treatment of combat-related PTSD in our active-duty military and recently discharged veterans are of significant national importance. The STRONG STAR Multidisciplinary PTSD Research Consortium will leverage the combined expertise of civilian, military, and Veterans Affairs clinicians and researchers to make major scientific advances in the prevention and treatment of combat-related PTSD.”

Alan Peterson, Ph.D.

University of Texas Health Science Center at San Antonio

TBI Multidisciplinary Research Consortium

Claudia Robertson, Baylor College of Medicine and **John Holcomb**, University of Texas Health Science Center at Houston

The TBI Multidisciplinary Research Consortium is composed of experienced TBI investigators from four academic institutions and from all of the major trauma facilities in the Houston-Galveston area operating within an existing cooperative framework, The Mission Connect Consortium. The goal of the joint efforts among these clinical and basic scientists is to reduce disabilities caused by mTBI by focusing on improving the diagnosis and treatment of mTBI. Specifically, the consortium will focus on standardization of animal models of mTBI using clinically relevant neurobehavioral end points, improvement of the diagnosis of acute and chronic mTBI, and development of new and innovative treatment strategies for mTBI, to include providing the preclinical and Phase I-II testing of treatments found to improve outcome. These innovative studies have the potential to lead to immediate improvements in the diagnosis and treatment of mTBI. The TBI consortium's lead Principal Investigators are Drs. John Holcomb, Ponnada Narayana, Paul Swank, Pramond Dash, Raymond Grill, and Andrew Papanicolaou (University of Texas Health Science Center at Houston); Drs. Claudia Robertson, Thomas Kent, Stephen LaConte, Matthew Rasband, Stelios Smirnakis, Harvey Levin, Andreas Tolia, Kimberly Tolia, Eli Mizrahi, and Michael Friedlander (Baylor College of Medicine); Dr. James Tour (Rice University); Drs. Ping Wu and Jose Perez-Polo (University of Texas Medical Branch, Galveston); and Dr. Brent Masel (Transitional Learning Center at Galveston).



The PH/TBI Program Fills Important Gaps ...By Supporting Innovative Concepts

Development of Biomimetic Scaffolding to Support Neural Stem Cell Treatment

Jun Chen, M.D., University of Pittsburgh

Dr. Chen is evaluating the use of biomimetic scaffolding for the long-term survival of transplanted stem cells following TBI. Neural stem cells (NSC) isolated from adult mice were incorporated into a type of extracellular matrix gel derived from the urinary bladder matrix (UBM). In the three-dimensional (3D) UBM, NSC exhibited better growth and differentiation and more morphological properties than NSC grown in Matrigel. Dr. Chen also synthesized an electrically conductive and electroactive scaffold made of the polymer polypyrrole (PPy). Neuroactive peptides p20 and p31, derived from the protein laminin, were incorporated into the polymer film as dopants. In preliminary in vitro experiments, electrical stimulation induced significantly more neuronal differentiation of NSC grown on PPy/p20 and PPy/p20-p31. This novel finding demonstrates that it is possible to manipulate the fate of NSC by electrical pulses applied via electroactive polymers. Last, when Dr. Chen implanted NSC grown on the 3D UBM scaffold into an animal model of TBI, positive immunohistochemical detection of nestin and MAP2 was found in only those animals receiving NSC grown on the UBM scaffold. Detection of these neuron-specific proteins indicates the survival and positive regeneration of NSC at the site of injury.

Implantable Microsystems for Anatomical Rewiring of Cortical Circuitry

Pedram Mohseni, Ph.D., Case Western Reserve University



Injury to the cerebral cortex causes loss of connectivity in the signaling junctions (synapses) between neurons. Functional synapses could be restored if nearby undamaged neurons could be guided to sprout new axons bypassing the injury site by directing the production of growth-promoting substances that naturally occur in a spatially limited area in injured brain tissue. Dr. Mohseni and his collaborating investigator, Dr. Randolph J. Nudo at the University of Kansas Medical Center, propose to provide this guidance in the form of electrical signals transmitted between cortical regions via an implantable neural microsystem. This system consists of paired electrodes, one to measure normal neural activity associated with a task such as limb movement and one to deliver synchronized neural signals to remote brain regions in a process called entrainment so that appropriate cortical connections can be reformed. A first-generation integrated device showed promising results when tested in an anesthetized rat model. Neural spikes from the somatosensory cortex of the brain were recorded successfully, and electrical stimulation of the primary motor cortex of the brain resulted in clear wrist movements.

Hormonal Regulation of Extinction: Implications for Gender Differences in the Mechanisms of PTSD

Laura Schrader, Ph.D., Tulane University

The most common diagnoses in male and female Soldiers seeking medical attention from VA medical facilities following service in Operation Iraqi Freedom/Operation Enduring Freedom are PTSD and depression. Studies focusing on PTSD and similar mental disorders indicate that women suffer from these disorders at approximately twice the rate of men. Although there is an increased incidence of PTSD and depressive disorders in women, the neurobiological mechanisms underlying gender differences of PTSD are poorly understood. Previous investigations indicate that changes in chromatin structure or epigenetic mechanisms involved in regulating gene transcription occur during learning and stress, an effect that may contribute to the development of specific pathologies. Given the ability of hormones to regulate gene expression, Dr. Schrader proposes that female hormones may play a role in the predisposition of females to PTSD via epigenetic mechanisms.

Pilot data generated in collaboration with Dr. Jill Daniel at Tulane University reveal that females exhibit increases in conditioned fear but decreases in extinction as compared with males. This suggests that a traumatic event has increased significance and is more difficult to suppress in females. Thus, using Pavlovian fear-conditioning and extinction paradigms as an animal model for the development of pathological fear in humans suffering from PTSD, Dr. Schrader is currently investigating whether estrogen predisposes females to increased fear learning and/or an

inability to extinguish fear. Further, Dr. Schrader is assessing whether blockade of histone deacetylase (HDAC) and modulation of chromatin structure via HDAC inhibitors such as sodium butyrate influences the extinction of fear memories. In addition, the hippocampus (a brain region involved in emotional, learning, and memory processes) is being investigated in animals exposed to fear conditioning to determine whether hormones mediate changes in chromatin structure and alter epigenetic effects that occur during the acquisition of fear memories. This research will provide a better understanding of hormonal regulation of fear acquisition and inhibition and may elucidate a mechanism contributing to the predisposition of females to an increased incidence of PTSD and other anxiety-related disorders.



The PH/TBI Research Program Fills Important Gaps

...By Developing Improved Treatments

A Randomized, Placebo-Controlled Trial of the Dopamine Beta Hydroxylase (DBH) Inhibitor, Nopicastat, for the Treatment of PTSD in OIF/OEF Veterans

Lori Davis, M.D., Tuscaloosa VA Medical Center



PTSD is a psychiatric condition that can develop following any traumatic life experience. Although about 7% to 8% of the population of the United States is likely to develop PTSD in their lifetime, its prevalence occurs at much higher rates in combat veterans, ranging from 10% to as high as 30%. A major complaint of military personnel serving in a combat zone during OIF/OEF is hyperarousal, which can interfere with social, occupational, and interpersonal functioning. Preclinical and clinical evidence suggests that increased noradrenergic activity contributes to the symptoms of hyperarousal experienced in patients with PTSD. DBH inhibitors function by inhibiting the DBH-mediated conversion of dopamine to neuronal noradrenaline, an effect that

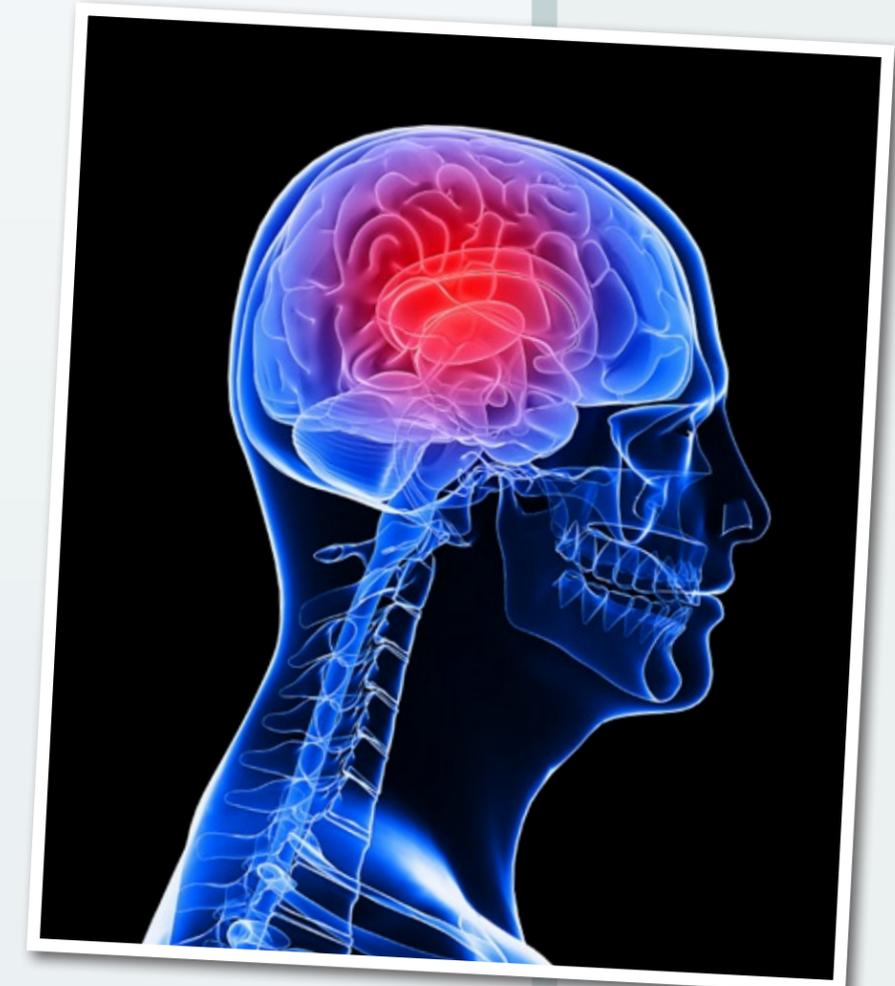
decreases noradrenaline release. As reducing noradrenaline has been shown to decrease symptoms of hyperarousal in PTSD patients, Dr. Lori Davis of Tuscaloosa VA Medical Center proposes that the DBH inhibitor nopicastat may be effective in reducing hyperarousal in PTSD patients.

Dr. Davis received funding to conduct a multisite Phase II randomized, double-blind, placebo-controlled clinical trial to assess the effectiveness of nopicastat for the treatment of hyperarousal in PTSD in OIF/OEF veterans. As a first step, Dr. Davis has initiated a 6-week, placebo-controlled pilot study of nopicastat for veterans with PTSD at three VA Medical Centers including Tuscaloosa, Houston, and Charleston. Once this pilot study has been completed, the full Phase II study will begin. For the full study, nopicastat or placebo will be administered under double-blind conditions (i.e., neither the doctor, assessor, or research participant will know the drug assignment) for 6 weeks followed by an 8-week open-label extension phase. During the 8-week extension phase, nopicastat will be given to all research participants to further assess improvement and safety. Those veterans who do not have a defined clinical response will be offered the standard first-line PTSD pharmacologic, paroxetine, in addition to the nopicastat for the 8-week extension phase. If successful, nopicastat will diminish the symptoms of PTSD and improve recovery for active military service members and combat veterans with PTSD.

A Randomized Controlled Trial of Medical Therapies for Chronic Post-Traumatic Headaches

Jay Erickson, M.D., Ph.D., Madigan Army Medical Center

Chronic post-traumatic headaches (PTHAs) develop in 20% of TBI patients, but no prospective clinical trials evaluating medical treatments for chronic PTHAs exist. Importantly, Dr. Jay Erickson of Madigan Army Medical Center (MAMC) at Fort Lewis Army Base in Washington state, received funding through an Investigator-Initiated Research Award to conduct a clinical trial to evaluate the efficacy of medical treatments for PTHAs. The study seeks to determine the effectiveness of propranolol, amitriptyline, and topiramate for treating chronic PTHAs in 240 patients meeting the International Classification of Headache Disorders diagnostic criteria for chronic PTHAs. The study participants, U.S. Army Soldiers, will be recruited from the Traumatic Brain Injury Program and the Neurology Clinic at MAMC. Participants are randomized to receive one of the three drugs or placebo for 3 months, and the primary outcome measure will be the number of moderate to severe headache days reported during the third month of treatment. Dr. Erickson will also measure the proportion of subjects with at least a 50% reduction in headache frequency and headache-related disability, PTSD symptom checklist score, and medication side effects. To date, 34 participants are enrolled in the study with no adverse effects or significant side effects reported.





Neurobiology of Sleep and Sleep Treatments in PTSD

Anne Germain, Ph.D., University of Pittsburgh School of Medicine

In addition to being a grave symptom of PTSD, sleep disturbance can also exacerbate other waking PTSD symptoms such as intrusive thoughts, hypervigilance, irritability, depression, and avoidance. A majority of military veterans with PTSD report sleep disturbances, such as frequent and distressing nightmares and insomnia, which often do not improve with the current recommended treatments for PTSD.

Dr. Anne Germain, an Investigator-Initiated Research Awardee, is studying how PTSD may have a direct impact on the regions of the brain that control sleep and wakefulness. To evaluate the neurobiology of PTSD during the sleep cycle and wakefulness, Dr. Germain compares polysomnographic sleep study results as well as sleep and wakeful positron emission tomography (PET) imaging scans from veterans both with and without PTSD. Study subjects who suffer from PTSD are then randomized into active medication or placebo treatment groups for an 8-week drug study. After drug treatment, sleep studies and PET scans are repeated. In this way, Dr. Germain can measure the efficacy of the drug treatment, identify other potential drug treatments, and explore biomarkers in the brain that may predict response to treatment and help guide clinicians treating sleep disorders. Findings from this study will provide novel insights into the neurobiological underpinnings of PTSD and contribute to the development and refinement of new and more effective treatment strategies for PTSD-related nightmares and insomnia and hasten the recovery of returning veterans with PTSD.

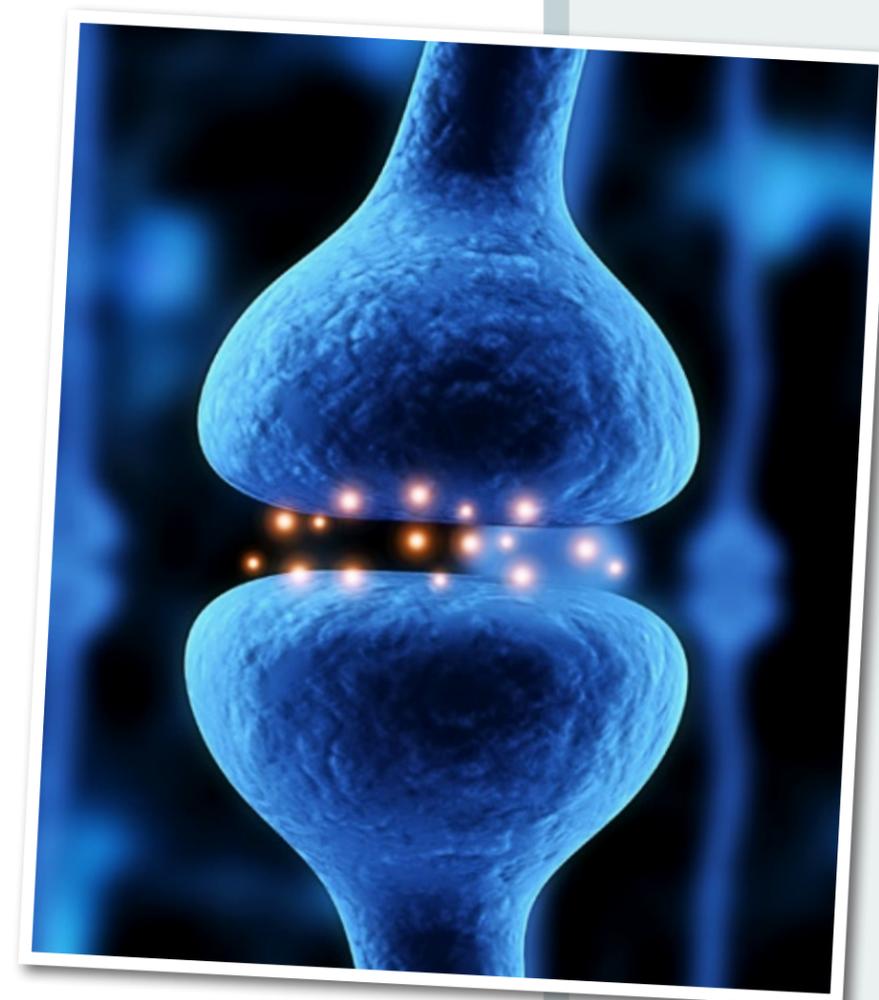
Small-Molecule Activators of the TRK Receptors for Neuroprotection

Nicholas J. Webster, Ph.D., Veterans Medical Research Foundation of San Diego

TBI is one of the major causes of mortality and morbidity in children and young adult civilians as well as among active duty military personnel. TBI is usually manifested in the loss of neurons within the region of the brain known as the hippocampus, an effect that can occur over a period of many days following the insult. Despite improvements in surgical treatment of the primary insult, there are currently no therapies that provide neuroprotection to mitigate this secondary or delayed damage subsequently leading to poor prognosis and chronic cognitive impairment. It is well known that the neurotrophins acting through the nerve growth factor Trk receptors promote survival of multiple neuronal cell types and stimulate in vitro

neuronal regeneration. Although preclinical and clinical findings suggest that neurotrophins are a promising therapy for TBI, they are not good drug candidates due to their poor pharmacokinetic behavior and bioavailability at the desired targets. Thus, much effort has been devoted to the search for novel small-molecule activators that will mimic the desired neuroregenerative responses of neurotrophins.

Dr. Webster, a recipient of an Intramural TBI Investigator-Initiated Research Award, is focusing on the development of such neuroprotective drugs that will activate the Trk receptors, leading to TBI-mediated neuronal cell death prevention and cognitive function improvement. During the first year of this award, Dr. Webster and his colleagues Dr. Stan Krajewski at the Burnham Institute for Medical Research and Dr. Michael Pirrung at the University of California, Riverside (1) identified the lead drug 5E5 and 38 other promising compounds based on their ability to activate the TrkB receptor, (2) initiated in vivo evaluation of the neuroprotective effects of 5E5 utilizing a mouse model of neurodegeneration, and (3) tested their lead drug 5E5 in a controlled cortical impact model for brain injury. The in vivo results indicated that treatment with 5E5 following the onset of cognitive impairments improved the ability of the mice to learn spatial information, exerted a neuroprotective effect, and also reduced the magnitude of the brain injury as measured by a smaller contusion area in the drug pretreatment group. Thus, further elucidation of the neuroprotective and pharmacokinetic properties of compounds that activate Trk receptors such as 5E5 may lead to the development of therapeutics for TBI that are easy and economical to manufacture and simple to administer.



The PH/TBI Research Program Fills Important Gaps

...By Advancing New Technologies

Better Testing for TBI in the Field

Jamshid Ghajar, M.D., Ph.D., Brain Trauma Foundation and Kristin Heaton, Ph.D., U.S. Army Research Institute of Environmental Medicine (USARIEM)

Dr. Jamshid Ghajar and researchers at the Brain Trauma Foundation, along with researchers from USARIEM and Foster-Miller, Inc., received funding from a TBI Advanced Technology–Therapeutic Development Award to further test the validity, reliability, and sensitivity of a clinically tested eye-tracking device and related software for mTBI called EYE-TRAC (Eye-Tracking Rapid Attention Computation). EYE-TRAC analyzes smooth pursuit eye movements to accurately detect sub-clinical attention and working memory deficits within seconds. The scientific rationale for the device’s accuracy in detecting attention impairments following TBI is based on the disruption of the attention network in the brain due to shearing of anterior white matter brain connections. Normally this attention circuit produces a predictive brain state rather than a reactive state, allowing a person to interact fluidly. Predictive eye-target tracking can measure the timing disruptions resulting from mTBI-induced shearing of the attention circuit that produces postconcussive “out-of-sync” symptoms. As such, EYE-TRAC can more accurately and in significantly less time (within seconds) diagnose mTBI as compared to current technologies. Thus far, Dr. Ghajar and colleagues are developing plans for the rugged outfitting of the device to be used as a portable, automated, goggle-like device. A prototype helmet-mounted device has been developed, and logistical issues relative to its use are being addressed. Thus, development of the eye-tracking device has progressed rapidly so far, and new subject testing also has been initiated. With this continued development, EYE-TRAC eventually can be used to assess fatigue in military personnel and distinguish PTSD from mTBI in the field or in forward medical facilities. The device also will be applicable for civilian use for diagnosing concussions from sports injuries and in emergency rooms where concussions from car crashes are a daily occurrence.



Treating Traumatic Memories

Roger K. Pitman, M.D., Massachusetts General Hospital, Harvard Medical School

A central problem in PTSD is excessively powerful and persistent memories of the traumatic event, which can cause substantial distress and disability. It has been shown that shortly after acquisition, enhancement of the consolidation of a conditioned fear response from an unstable to a stable state by stress hormones can be mitigated pharmacologically with antistress agents. However, a limited window of opportunity exists to influence the consolidation of the event into long-term memory. Historically, undoing a memory that has already been consolidated has been considered impossible. However, recent developments in animal research suggest that reactivation (retrieval) of a consolidated memory can return it to an unstable state, from which it must be restabilized to persist. Certain drugs can block this restabilization. Reconsolidation blockade may re-open the window of opportunity for weakening a traumatic memory with antistress drugs.

Under an FY07 PTSD Advanced Technology Therapeutic Development Award, Dr. Roger Pitman and his team are investigating memory reconsolidation in animals and humans in an attempt to identify and develop novel drug approaches that may be effective for veterans with PTSD. Candidate drugs are initially being screened for their ability to block reconsolidation of conditioned freezing in animals, as well as to undo accompanying long-term potentiation in brain, viz., amygdala, slices. Promising candidate drugs will then be tested for their ability to reduce physiological responses to traumatic cues in trauma-exposed humans following a single postreactivation/drug treatment session. Finally, effectiveness in reducing PTSD symptoms in multiple post-reactivation sessions will be pilot tested in PTSD patients. Reconsolidation-blocking drug treatments that show a substantial PTSD symptom reduction effect will become candidates for inclusion in full-blown randomized clinical trials. Initial animal studies are currently under way. In early results, the drug mifepristone has been found to block the reconsolidation of cued fear conditioning in animals, and it has been slated to be moved on to the single-session human experiment.



The PH/TBI Program Fills Important Gaps

...By Investing in Tomorrow's Leaders

Pilot Trial of Inpatient Cognitive Therapy for the Prevention of Suicide in Military Personnel with Acute Stress Disorder or Post-Traumatic Stress Disorder

Marjan Holloway, Ph.D., Uniformed Services University of the Health Sciences

PTSD is a significant public health problem and a prevalent mental disorder diagnosed in military service members exposed to combat service. Research has shown there is a strong association between PTSD and suicide and, in fact, PTSD shows the strongest association with suicide behavior of any anxiety disorder.

Dr. Marjan Holloway, a New Investigator Awardee, is working to develop, implement, and evaluate an evidence-based, inpatient, cognitive-behavioral care plan for service members and their beneficiaries with symptoms of either acute stress disorder or PTSD who are hospitalized following a suicide attempt. Dr. Holloway proposes to deliver a brief, targeted intervention to individuals who are admitted to Walter Reed Army Medical Center following a recent suicide attempt. The intervention will include six 1-hour therapy sessions in the first 3 days after study enrollment. Study subjects also will be assessed via face-to-face, phone, and web-based interviews at 1-, 2-, and 3-month intervals post-treatment. Dr. Holloway hypothesizes that targeting at-risk individuals immediately following a suicide crisis will reduce the likelihood of future complications.

As a result of this study, Dr. Holloway hopes to produce a new manual of Post-Admission Cognitive Therapy and significantly reduce the number of subsequent suicide attempts by suicidal individuals. In addition, she proposes that such an intervention may mitigate psychological risk factors associated with suicide such as depression, hopelessness, suicide ideation, and PTSD symptoms. If successful, the development and dissemination of an innovative, inpatient-focused intervention for traumatized individuals with suicidal behavior will significantly contribute to national and military suicide prevention objectives.



The Vision for FY09

In FY09, approximately \$40.6M is available to support PH/TBI research. An investment strategy was developed that emphasizes a focus on innovative projects that will have the potential to make a significant near-term impact on improving the function, wellness, and overall quality of life for warriors, veterans, families, and caregivers. The program offered 3 award mechanisms that provided support to address priorities outlined in the FY09 PH/TBI Congressionally Directed Topic Areas. Approximately 16–17 awards are anticipated.

Focus	Award Mechanism	Proposals Received
Technology and Therapeutic Development 	<u>Advanced Technology/Therapeutic Development Award</u> : Supports the assessment of scientific and/or military field deployment feasibility for promising new products, pharmacologic agents, behavioral interventions, devices, clinical guidance, and/or emerging approaches or technologies	74
Innovative Research 	<u>Concept Award</u> : Supports the initial exploration of innovative, untested, high-risk, high-gain, and potentially groundbreaking concepts in PH and/or TBI research	212
	<u>Investigator-Initiated Research Award</u> : Provides support for research studies that focus on any phase of research from basic laboratory through translational research	143



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