U.S. ARMY MEDICAL RESEARCH & MATERIEL COMMAND

Militarily-Relevant Peer Reviewed Alzheimer's Disease Research Program September Update

Anthony Pacifico, PhD

The views expressed in this briefing are those of the author and do not reflect official policy or position of the Department of the Army, Department of Defense or the U.S. Government.

April 2014

Program Mission

The mission of the MRPRA is two-fold. The MRPRA seeks to 1) build an integrated program devoted to understanding the association between Traumatic Brain Injury (TBI) and Alzheimer's disease (AD), and 2) to reduce the burden on those affected by TBI-AD symptoms, especially in the military community.

MRPRA Overarching Challenges

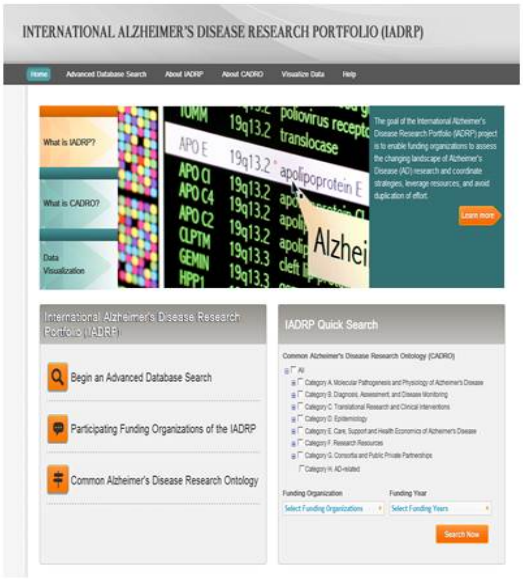
Consistent with the program's overall goals, this MRPRA funding opportunity requires applications to address only one of the following MRPRA overarching challenges:

- ***The paucity of research resources to examine the interrelationship between TBI and subsequent AD for military veterans that is suitable to inform or create large-scale clinical studies.***
- ***The need for technologies, tests, interventions or devices with the potential to diagnose AD at its earliest stages.***
- ***The need for technologies, tests, interventions or devices with the potential to directly benefit individuals suffering from the symptoms of TBI or AD with respect to quality of life for those affected.***
- ***The identification and validation of clinical best practices to directly benefit individuals suffering from the symptoms of TBI or AD, while reducing caregiver burden.***

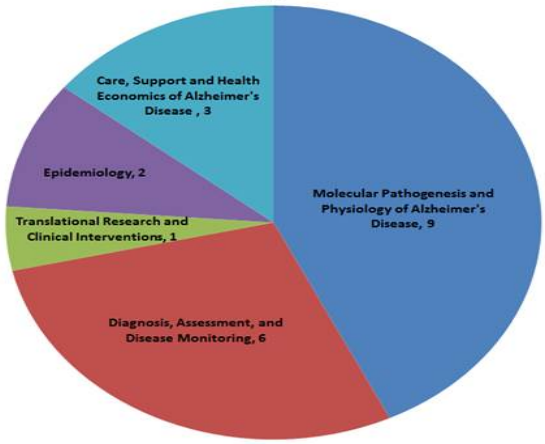
Focus Areas: The Way Ahead

- **Imaging:** *Development of anatomic and molecular imaging strategies that will address the MRPRA Overarching Challenges.*
- **Genomics/Proteomics:** *Genetic, Proteomic and epigenetic studies (or technologies) intended to develop research resources in accordance with the MRPRA Overarching Challenges.*
- **Quality of Life:** *Technologies, tests, interventions, studies or devices that will positively impact the quality of life of those affected by the symptoms of TBI or AD.*
- **Pathology of Tau:** *Novel research and technologies dedicated to unraveling the basic pathobiological mechanisms of Tau.*

Portfolio Analysis via IADRP



FY 11/12 MRPRA Projects Broken Down by IADRP Ontology Criteria

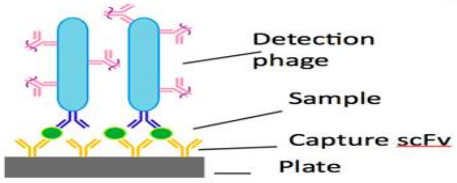


Dr. Michael Sierks

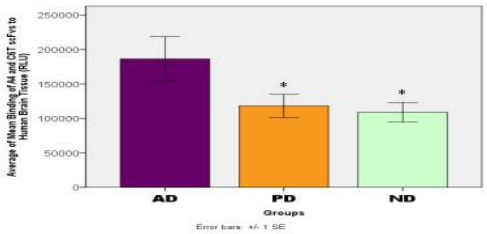
Arizona State University

"Oligomeric neuronal protein aggregates as biomarkers for TBI and AD"

- Novel, and potentially cost-effective strategy for detecting the early events after traumatic brain injury (TBI) and for long-term monitoring.
- Technology can also be used for probing the formation of plaques.
- Library of nanobodies for:
  - oligomeric beta-amyloid aggregate species
  - a-synuclein aggregate species
  - oligomeric tau
  - fibrillar beta-amyloid and a-syn



Cumulative Oligomeric Abeta in Human Brain Tissue



The binding intensities of A4 and C6T to the human brain tissue samples were averaged.
* = Results significant to AD group.

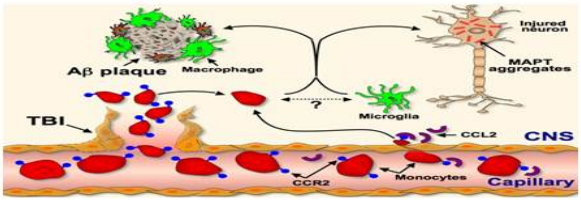
Early work showing the detection of a toxin specific to Alzheimer's disease (AD). The toxin, Abeta was not detected in brain tissue from Parkinson's patients (PD) when compared to controls (ND).

Dr. Bruce Lamb

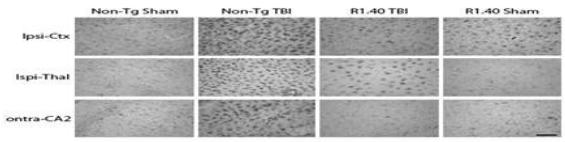
Cleveland Clinic

"Novel Genetic Models to Study the Role of Inflammation in Brain Injury-Induced Alzheimer's Pathology"

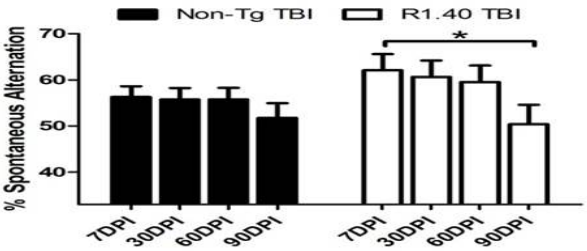
- Project tracks two different sources of inflammation; namely the peripheral monocytes of the bloodstream, and the microglia innate to the brain.
- Using an injury model with mice that overproduce beta-amyloid, Dr. Lamb showed that beta-amyloid exacerbated the growth of the injury compared to controls.
- In the Thalmus of these mice the immune response was altered.



Model of How the Inflammatory Cascade Following TBI Impacts AD Pathologies



Altered Immune Reaction in a Mouse Model of AD (R1.40) Compared to Non-Transgenic Controls in Various Brain Regions Following TBI



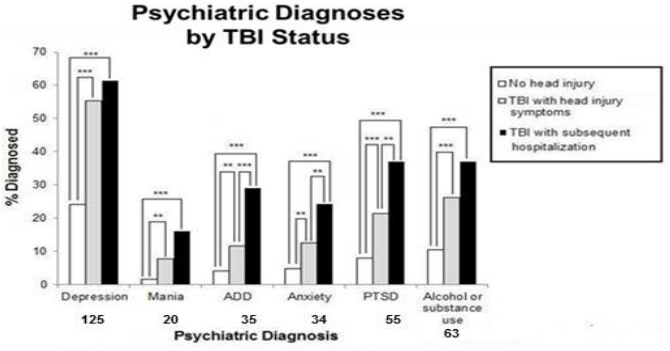
Worsened Age-Related Cognition in a Mouse Model of AD (R1.40) Compared to Non-Transgenic Controls in Following TBI

Dr. Kristine Yaffe

Northern California Institute for Research and Education (NCIRE)

"Endophenotypes of Dementia Associated with Traumatic Brain Injury (TBI) in Retired Military Personnel"

- Dr. Yaffe's team surveyed nearly 300 veterans at two veteran retirement homes which were located in Washington D.C. and Northern California.
- 56% of those surveyed had a history of TBI.
- TBI was associated with psychiatric symptoms such as depression, anxiety, and post-traumatic stress disorder (PTSD).
- Veterans with TBI had problems answering orientation questions (a sign of cognitive impairment): 23.3% for the hospitalization group, 18.3% for the TBI group, and 15.4% for non-TBI group. (n=54)
- Veterans with TBI were also more likely to have subjective memory complaints (26.7% for TBI hospitalization group, 20.6% for the TBI group, 10.8% for the non-TBI group). (n=156)
- A total 114 patients reported multiple diagnoses.
- Data will be correlated with structural MRI.



Dr. Michael Weiner

Northern California Institute for Research and Education (NCIRE)

"Effects of Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD) on Alzheimer's disease (AD) in Veterans using Imaging and Biomarkers from the Alzheimer's Disease Neuroimaging Initiative (ADNI)"

- Use the ADNI machinery to understand TBI and neurodegenerative disease in Vietnam-era veterans.
- Study Vietnam-era population to understand the future of veterans returning from OIF/OEF.
- More than 10,000 veterans were contacted to form the cohort.
- Study#1 (2012): Look at Vietnam Veterans (n=195) with signs of TBI and/or PTSD and perform a comprehensive battery of neuroimaging, CSF analyses, and neuropsychological testing.
- Study#2 (2013): Look at Vietnam Veterans (n=195) with signs of MCI.
- Both studies are accruing patients across all 19 sites.
- Data will become available via the ADNI database.

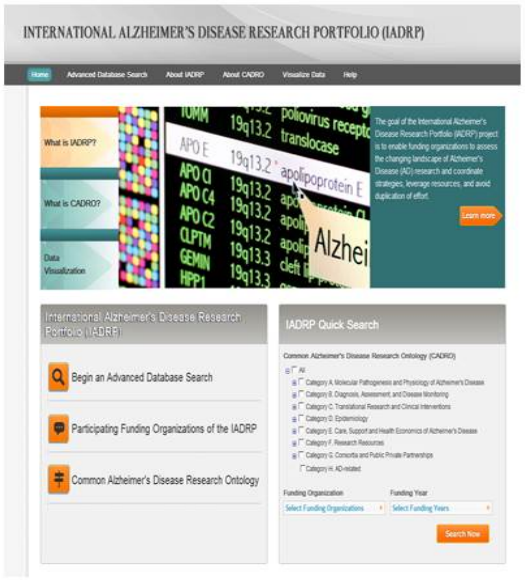
DOD ADNI Clinic Sites

Clinic Name	Principal Investigator	City, State
Banner Sun Health Research Institute	Marwan Sabbagh, MD	Sun City, Arizona
University of California, Irvine	Ruth Mulnard, D.N.Sc.	Irvine, CA
University of California, San Diego	James Brewer, MD, PhD	La Jolla, CA
University of Southern California	Lon Schneider, MD	Los Angeles, CA
Stanford University	Jerome Yesavage, MD	Palo Alto, CA
University of California, San Francisco	Howard Rosen, MD	San Francisco, CA
Georgetown University	Brigid Reynolds, RN, MSN, NP	Washington, DC
Howard University	Thomas Obisesan, MD	Washington, DC
Wien Center for Clinical Research	Ranjan Duara, MD	Miami Beach, FL
Premiere Research Institutes	Carl Sadowsky, MD	West Palm Beach, FL
Rush University	Debra Fleischman, PhD	Chicago, IL
Brigham and Women's Hospital	Gad Marshall, MD	Boston, MA
Duke University	P. Murali Doraiswamy, MD	Durham, NC
Columbia university	Yaakov Stern, PhD	New York, NY
Weill Cornell University	Norman Relkin, MD, PhD	New York, NY
University of Rochester Medical Center	Anton Porsteinsson, MD	Rochester, NY
Medical University of South Carolina	Jacobo Mintzer, MD	North Charleston, SC
University of Washington Medical Center	Elaine Peskind, MD	Seattle, WA
University of Wisconsin	Sterling Johnson, PhD	Madison, WI

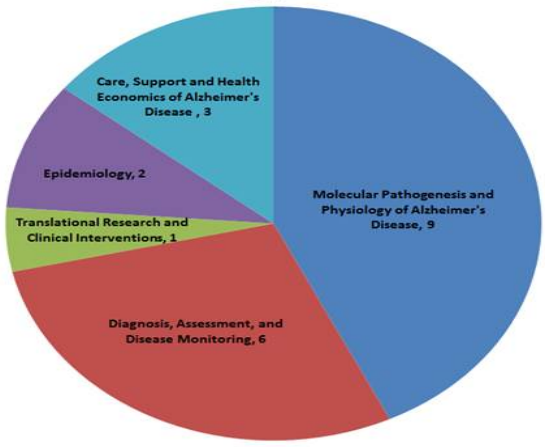
http://www.adni-info.org/DOD.aspx

http://adni.loni.usc.edu/data-samples/access-data/

Portfolio Analysis via IADRP



FY 11/12 MRPRA Projects Broken Down by IADRP Ontology Criteria



Program Steering Comittee

FY13 PSC Members:

Dr. Anthony Pacifico (Department of the Army (DOA))
Dr. Robert Kane (DOA)
CAPT Jack Tsao (Department of the Navy (DON))
Col (R) Mike Jaffee (University of Virginia)
Ms. Ashley Fisher (DOA)
Dr. Laurie Ryan (National Institute on Aging (NIA))
Dr. Neil Buckholtz (NIA)
Dr. Bryan Traynor (NIA)
Dr. Nina Silverberg (NIA)
Dr. Stuart Hoffman (US Dept. of Veterans Affairs)
Dr. Roderick Corriveau (National Institute of Neurological Disorders and Stroke (NINDS))
Dr. Deborah Babcock (NINDS)
Dr. Valerie Trabosh (DOA)
LTC Sarah Goldman (DOA)
Dr. Brenda Bart-Knauer (DOA)

FY13 External Advisory Board Members:

Dr. Maria Carillo (Alzheimer's Association)
Dr. Heather Snyder (Alzheimer's Association)
COL Dallas Hack (DOA)
COL John Scherer (DOA)
Dr. Kenneth Curley (DOA)
CAPT Doug Forcino (DON)

Contact Info

Dr. Anthony Pacifico
Program Manager, Militarily Relevant Peer-Reviewed Alzheimer's Disease Research Program
United States Army Medical Research and Materiel Command
Anthony.M.Pacifico.CIV@mail.mil