VA Biorepository Brain Bank
Gulf War Veterans’ Illnesses Biorepository
VA Boston

Bertrand Huber, M.D., Ph.D.
VA Boston Healthcare System
Boston University School of Medicine

Meeting of the Research Advisory Committee on Gulf War Veterans’ Illnesses
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VA Biorepository Brain Bank (VABBB) Background

• The VA Biorepository Brain Bank (VABBB) was developed as an amyotrophic lateral sclerosis (ALS) brain bank in 2006 by VA in response to findings that linked ALS to deployment to the Persian Gulf and military service in general.

• The VABBB is coordinated at VA Boston Healthcare System (VABHS).

• Veterans/next-of-kin receive regular follow-up from VABBB staff via telephone and mailed surveys.

• Tissue is analyzed, processed and stored at the Southern Arizona VA Healthcare System (SAVAHCS) in Tucson, AZ.

• Diagnostic neuropathological analyses are conducted at VABHS.

• Tissue/data releases to investigators are ongoing.
• Given the development of the VABBB as a national tissue recovery model, this model was adapted to develop the Gulf War Veterans’ Illnesses Biorepository (GWVIB) brain bank.

• New challenges for the development of the GWVIB were:
  – GWVIB open to all 1990-1991 Gulf War Veterans regardless of whether they receive care at VA
  – Research tissue needs of investigators
  – Recruitment and enrollment procedures
  – Data acquisition and management
  – Ongoing follow-up
Research tissue needs of investigators

The value of postmortem CNS tissue had already been established via feedback from the Gulf War Illness experts and the literature:

- Accurate diagnoses of neurodegenerative diseases can only be obtained through post-mortem pathology
- Necessary for clinicopathological correlation
- Human tissue is required to study human disease and to test the relevance of results from animal models
- High quality DNA, RNA, and protein required for accurate and reproducible results
- May aid in the understanding of disease, the discovery of new diagnostic targets, and the development of therapeutics
Research tissue needs of investigators

- The need for non-CNS tissue had not been established
- Collecting non-CNS tissue presented considerable logistical hurdles
- Poll conducted by VABBB of 33 VA Gulf War researchers did not presently support the need to collect non-CNS tissue
- Based on this feedback it was decided to begin the GWVIB as a CNS tissue biorepository
- Non-CNS tissue collection could be considered in the future if the need arises
GWVIB Site Responsibilities

• Boston
  – Operations and data coordinating center
  – Recruitment/enrollment/follow-up
  – Pager coverage/tissue recovery coordination
  – Medical informatics
  – Data management
  – Diagnostic neuropathology

• Tucson
  – CNS tissue processing/storage
  – CSF processing/storage
  – Tissue data management
  – Tissue requests/disbursements
GWVIB Recruitment

- Web site
  https://www.research.va.gov/programs/tissue_banking/gwvib/
- Brochure
- Nationwide toll-free number- 855-561-7827
- Postings on GW Veteran web sites and newsletters
- Outreach to GW Veteran organizations
- Social media
- Other GWV treatment centers/research projects
GWVIB Web Site

http://www.research.va.gov/programs/tissue_banking/gwvib/
GWVIB Brochure

Gulf War Veterans’ Illnesses Biorepository Brain Bank
Department of Veterans Affairs

For more information, contact 888-661-7827
www.research.va.gov/programs/tissue_banking/GWVIB

VETERANS HEALTH ADMINISTRATION
VABBB Historical Enrollment Map (GWVIB Enrollees Shown in Orange)

States and U.S. Territories Where Veterans Have Enrolled in the VABBB

- Participants enrolled in the ALS Biorepository Brain Bank
- Participants enrolled in the PTSD Biorepository Brain Bank
- Participants enrolled in the Gulf War Illness Biorepository Brain Bank
GWVIB Data Acquisition

• Data collected at enrollment
  – Health information via telephone interview and mailed survey
  – Telephone Interview of Cognitive Status – Modified (TICSm)
  – Medical history from VA electronic medical record if present

• Data collected during semi-annual follow-up
  – Updated medical history and contact information via telephone interview and mailed survey
  – TICSm
GWVIB Health Survey

Domains assessed:

– Demographics and physical features
– Gulf War Veterans’ illnesses symptom checklists
  • Gulf War illness by Kansas case definition and chronic multisymptom illness by Fukuda case definition
– Military and occupational exposures (SNAC-Short Form)
– Health history and healthcare use
– Family health history
– Military service and combat exposure
– Tobacco and alcohol use
GWVIB Tracking and Tissue Recovery

- Annual or less if health is failing
- Blood samples collected on willing Boston enrollees and processed/stored in Tucson
- Tissue recovery portfolio development:
  - Arrange for tissue recovery
- Brain, spinal cord & cerebrospinal fluid recovery
  - 24/7 coverage with delivery to Tucson by special door-to-door courier service
Blood collection strategy for GWVIB project

21 mL (4 tsp) blood

PAXgene DNA
8.5 mL
PON1 and APOE genotyping

cryopreservation

PAXgene RNA
2.5 mL
plasma

Plasma/PBMC
10 mL
PBMC

VETERANS HEALTH ADMINISTRATION
Multiple formats allow for a diverse range of study possibilities

DNA: Gene sequencing and polymorphism studies

RNA: Gene expression and microRNA studies

Plasma: Blood protein and cytokine studies

PBMCs: Cellular studies
Genotyping GWVI Blood

PON1 and APOE genotyping allows investigators to select and pool specimens for more targeted studies.

**PON1:**
Serum enzyme that detoxifies organophosphate poisons

Gene contains 2 polymorphisms which can result in 4 isozymes

1. Position 192 (Q to R)
2. Position 55 (L to M)

*R* isozyme more efficiently hydrolyzes paraoxon produced from the insecticide parathion

*Q* isozyme more efficiently hydrolyzes diazoxon and nerve gases sarin and soman

*L/M* polymorphism contributes to genetic susceptibility to paraoxon
Genotyping GWVI Blood

APOE:
A major cholesterol carrier and maintains lipid homeostasis in the brain
APOE is polymorphic at 2 single nucleotides
  1. rs429358
  2. Rs7412
These polymorphisms result in 3 alleles
  1. ε2
  2. ε3
  3. ε4
ApoE isoforms determine risk levels for vascular and neuro-degenerative diseases
GWVIB Cohort Characteristics (n=15 so far)

Table 1. Cohort Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age, mean (SD), y</td>
<td>51.1 (7.4)</td>
</tr>
<tr>
<td>Age range, y</td>
<td>44 - 70</td>
</tr>
<tr>
<td>Men (%)</td>
<td>80</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
</tr>
<tr>
<td>High school/GED</td>
<td>10</td>
</tr>
<tr>
<td>Some college</td>
<td>40</td>
</tr>
<tr>
<td>Associates degree</td>
<td>10</td>
</tr>
<tr>
<td>Bachelor's degree</td>
<td>20</td>
</tr>
<tr>
<td>Master's degree</td>
<td>20</td>
</tr>
<tr>
<td>Military exposures (%)</td>
<td></td>
</tr>
<tr>
<td>Combat exposure</td>
<td>70</td>
</tr>
<tr>
<td>Blast exposure</td>
<td>30</td>
</tr>
<tr>
<td>Pyridostigmine Bromide pills (sure/unsure)</td>
<td>80/20</td>
</tr>
<tr>
<td>Chemical/biological warfare agents (sure/unsure)</td>
<td>40/60</td>
</tr>
<tr>
<td>Anthrax vaccine (sure/unsure)</td>
<td>70/30</td>
</tr>
<tr>
<td>Health history (%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 concussion</td>
<td>70</td>
</tr>
<tr>
<td>Traumatic brain injury diagnosis - ever</td>
<td>20</td>
</tr>
<tr>
<td>Memory loss diagnosis - ever</td>
<td>50</td>
</tr>
<tr>
<td>Cancer diagnosis-ever</td>
<td>30</td>
</tr>
<tr>
<td>Chronic Multisymptom Illness – Fukuda critera (%)</td>
<td>70</td>
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</tbody>
</table>
Effects of Sarin Exposure: Khamisiyah GWV

Gulf War Illness by Kansas case definition (Steele)

**Average Kansas score**
(Highest possible score = 87)

- DoD-reported Khamisiyah GWV
- Khamisiyah GWV report more GWI symptoms
Effects of Sarin Exposure: Khamisiyah GWV

Kansas case definition scores (% of total) by symptom domain

- Khamisiyah GWV report relatively more GI & respiratory symptoms
GWVIB Results Summary

- Gulf War Veterans who have enrolled are exhibiting high rates of symptoms
- 70% have chronic multisymptom illness by Fukuda criteria
- Khamisiyah Veterans exhibit greater rates of Gulf War Illness symptoms than those not at Khamisiyah
  - Khamisiyah Veterans exhibit higher rates across all symptom domains
  - GI and respiratory symptoms exhibit greatest relative difference
GWVIB Accomplishments

Outreach
• Extensive outreach via multiple outlets
• Web site
• Boston area GWI researcher collaboration with web site in development

Recruitment/enrollment
• Development of national telephone/mail consenting and data collection model
• 50% success rate in consenting referrals when we are able to make telephone contact
GWVIB Challenges

**Outreach and recruitment**

- Despite extensive national outreach, enrollment thus far has been disappointing.
- Current tensions between GWV and VA has affected GWV enthusiasm to participate in VA research and research without a treatment focus.
- Our focus has been to encourage GWV to enroll even though their future donation may be many years away.
  - Longitudinal health data is useful now and for subsequent tissue donation.
  - Blood donation now can be used for current studies.
GWVIB as a Resource for Other GWI Research

GWVIB can provide value added collaborations to current and future studies of GWI to provide:

• Long-term longitudinal follow-up
• Blood processing and storage
• CNS tissue samples

GWVIB can provide tissue and data to collaborating studies via data use/ material transfer agreements

Cost-effective as infrastructure in place
Thank you