

Award Number: W81XWH-22-1-1081

TITLE: Department of Defense Alzheimer's Disease Blood-Testing Initiative (DOD-ADBI): A Study to Accelerate Blood-Based Diagnosis of Alzheimer's in Veterans

PRINCIPAL INVESTIGATOR: Dr. Raquel Gardner, MD

CONTRACTING ORGANIZATION: Medical Research Infrastructure Development by Sheba

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14. ABSTRACT: With the recent FDA-approval of the amyloid-targeting drug, Aducanumab, clinical practice has entered a new era of biomarkerguided diagnosis and treatment of Alzheimer's disease (AD). FDA-approval of other amyloid-targeting drugs is expected soon. Scalable screening for brain amyloid and AD-associated tau (AD-tau) to inform allocation of these costly drugs is critical. Cerebrospinal fluid and PET studies are considered gold-standard for diagnosis of brain amyloid and tau in living patients, but will not be feasible for community-based screening. Emerging blood biomarkers may facilitate scalable diagnosis of AD per unbiased "A/T" (amyloid-tau) biomarker categorization. Unfortunately, prior studies of accuracy of these blood tests were done in non-Veterans, mostly in highly selected cohorts with minimal comorbidities. Traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), and cerebral small vessel disease (CSVD) are common in Veterans and may alter accuracy of blood biomarkers for AD diagnosis. While these military relevant exposures (MREs) are associated with increased risk for dementia, clinical and pathological features are more consistent with non-AD. For example, the major finding of the DoD Alzheimer's Disease Neuroimaging Initiative (DoDADNI) study in Vietnam Veterans is that TBI and PTSD are associated with high rates of non-amnestic MCI but are not associated with AD biomarkers. It is unknown whether or how these highly prevalent MREs, atypical clinical features, and non-AD pathologies will effect blood-based AD diagnosis in Veterans. Due to atypical clinical features, it is also unclear which Veterans should be prioritized for AD biomarker testing in the first place. Goals: To address these gaps we will validate accuracy of leading A/T blood biomarkers in Veterans, determine whether MREs alter the relationship between A/T blood and neuroimaging biomarkers, and identify clinical predictors of A/T biomarker positivity. We will cost-efficiently leverage and extend DoD-ADNI (W81XWH-14-1-0462; PI Weiner, co-I on this proposal; 9/14-9/21), which collected amyloid PET, tau PET, and blood on 280 Vietnam Veterans with normal cognition (80%) and MCI. To expand validation to symptomatic Veterans, we will additionally recruit 100 Veterans with MCI and mild dementia from 2 VA Memory Clinics. Both cohorts will have high rates of prior TBI, PTSD, and CSVD.					
15. SUBJECT TERMS NONE LISTED					
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- 1. Accomplishments:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project identify these dates and show actual completion dates or the percentage of completion.

During Y1 our major goals were:

1. Launch enrollment into DoD-ADBI Cross-Sectional Cohort Study at all 3 sites.
2. Run assays on banked DoD-ADNI blood.

What was accomplished under these goals?

For this quarterly reporting period only describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided.

- 1) Major Activities: We obtained sIRB approval and Helsinki approval for all parts of the study at all sites. We are just waiting for final OHRO approval. We built the REDCap database to house the Aim 1 cohort study data. We began cleaning and analyzing existing ADNI-DOD data in preparation for the Aim 2 analysis on existing ADNI data. We have nearly completed the translation and back-translation of study forms that are not already available in Hebrew; most key assessments are already available in validated Hebrew translations. We requested and received permissions for all needed cognitive assessments in English and Hebrew for those that are copyrighted. We finalized the order of administration of cognitive assessments at each site. We set up the MRI protocol at each site. We set up payment/ordering of the amyloid PET radiotracer for each site. We set up a subcontract to NCRAD to produce our blood collection kits for both U.S. sites and set up payment for Sheba to produce the same blood collection kits for the Sheba Israel site. We finalized the contract with Quanterix to purchase kits to run ptau217 and NFL in Les Shaw's lab. We established a new collaboration with Washington University as they also requested existing ADNI-DOD blood specimens specifically to run Mass Spec assays for multiple ptau isoforms and abeta 42/40 and so we are synergizing our projects and will run those assays at WashU instead of at C2N (of note, the C2N mass spec assay was developed at WashU).
- 2) Specific Objectives: We have completed 90% of planned activities. We are extremely close to launching Aim 1 enrollment at all sites and to beginning to analyze existing ADNI-DOD samples for Aim 2.
- 3) Results/Outcomes: We have no new results. Data presented in the DoD-ADBI grant proposal and presented in the Y1Q1 progress report were presented orally at AD/PD 2023 in Gothenburg Sweden in March 2023 and are being prepared for submission as an original article to a peer reviewed journal.
- 4) Other Achievements/Goals Not Met: Awaiting final OHRO approval. Awaiting shipping of blood collection kits from NCRAD to U.S. sites. Awaiting shipping of Quanterix assay kits to UPenn. Awaiting shipping of ADNI-DOD specimens to WashU for analysis.

(a) Human Use Regulatory Protocols

TOTAL PROTOCOLS: State the total number of human use protocols required to complete this project (e.g., 5 human subject research protocols will be required to complete the Statement of Work.”). If not applicable, write “No human subjects research will be performed to complete the Statement of Work.”

PROTOCOL(S): List the identifier and title for all human use protocols needed to complete the project. Include information about the approved target number for clinical significance, type of submission, type of approval with associated dates, and performance status.

The following format shall be used:

Protocol (1/3 of total):

Protocol [HRPO Assigned Number]:

Title:

Target required for clinical significance:

Target approved for clinical significance:

Submitted to and Approved by:

Provide bullet point list of protocol development, submission, amendments, and approvals (include IRB in addition to HRPO).

Status:

Report (i) progress on subject recruitment, screening, enrollment, completion, and numbers of each compared to original planned target(s), e.g., number of subjects enrolled versus total number proposed; (ii) amendments submitted to the IRB and USAMRMC HRPO for review; and (iii) any adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation.

TOTAL PROTOCOLS: 3 (Sheba Medical Center Helsinki Committee, University of California San Francisco sIRB, and DoD Office of Human Research Oversight OHRO)

PROTOCOL (1 of 3): OHRO

Protocol E03207.1a

Title: **Sheba Phase 1 of DoD-ADBI (existing data/specimens)**

Target required for clinical significance: N/A

Target approved for clinical significance: N/A

SUBMITTED TO AND APPROVED BY:

- OHRO Log #E03207.1a: Approved on 03/14/2023
- Sheba Medical Center Helsinki #9706-22-SMC: Approved on 11/09/2022.

STATUS:

- (i) Number of subjects recruited/original planned target: N/A; this protocol uses existing data
Number of subjects screened/original planned target: N/A; this protocol uses existing data
Number of patients enrolled/original planned target: N/A; this protocol uses existing data
Number of patients completed/original planned target: N/A; this protocol uses existing data

(ii) Report amendments submitted to the IRB and USAMRMC OHRO for review: N/A

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: N/A

PROTOCOL (2 of 3): OHRO

Protocol E03207.2x

Title: **Sheba Phase 2 of DoD-ADBI (prospective cohort)**

Target required for clinical significance: N=30

Target approved for clinical significance: N=30

SUBMITTED TO AND APPROVED BY:

- OHRO: Under review
- Sheba Medical Center Helsinki Committee: Approved

STATUS:

- (i) Number of subjects recruited/original planned target: 0/20
Number of subjects screened/original planned target: 0/20
Number of patients enrolled/original planned target: 0/20
Number of patients completed/original planned target: 0/20

(ii) Report amendments submitted to the IRB and USAMRMC OHRO for review: N/A

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: N/A

PROTOCOL (3 of 3): OHRO

Protocol E03207a,b,c

Title: **UCSF/OHSU/UPenn sIRB DoD-ADBI (prospective cohort)**

Target required for clinical significance: N=80

Target approved for clinical significance: N=80

SUBMITTED TO AND APPROVED BY:

- OHRO: Approved
- UCSF IRB #22-36139: Approved as single-site study on 12/12/2022.
- UCSF sIRB: Approved.

STATUS:

- (i) Number of subjects recruited/original planned target: 0/80
Number of subjects screened/original planned target: 0/80
Number of patients enrolled/original planned target: 0/80
Number of patients completed/original planned target: 0/80

(ii) Report amendments submitted to the IRB and USAMRMC HRPO for review: N/A

(iii) Adverse event/unanticipated problems involving risks to subjects or others and actions or plans for mitigation: N/A

(b) Use of Human Cadavers for Research Development Test & Evaluation (RDT&E), Education or Training

TOTAL ACTIVITIES: None. Cadavers will not be used for this project.

ACTIVITIES: N/A

(c) Animal Use Regulatory Protocols

TOTAL PROTOCOL(S): None. Animals will not be used for this project.

N/A

What do you plan to do during the next reporting period to accomplish the goals and objectives?

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

1. Launch enrollment into DoD-ADBI cohort
 2. Begin analyzing existing banked ADNI-DOD samples.

2. Products: List any products resulting from the project during the reporting period. If there are no products to report for the current quarter, state "Nothing to report."

Examples of products include:

- *publications, conference papers, and presentations;*
- *website(s) or other Internet site(s);*
- *technologies or techniques;*
- *inventions, patent applications, and/or licenses; and*
- *other products, such as data or databases, biospecimen collections, germplasm, audio or video products, software, models, educational aids or curricula, instruments or equipment, data and research material, clinical or educational interventions, or new business creation.*

1. Oral presentation delivered at AD/PD 2023 in Gothenburg Sweden in March 2023: Lesman-Segev O, La-Joie R, Yaffe K, Weiner M, Silbert L, Shaw L, Gardner R. Burden of cerebral small vessel disease modifies relationship between plasma abeta 42/40 and amyloid PET

3. Participants & Other Collaborating Organizations

What individuals have worked on the project?

Provide the following information for: (1) Project Directors (PDs)/ PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

Provide the name and identify the role the person played in the project. Indicate the nearest whole person month (Calendar, Academic, Summer) that the individual worked on the project. Show the most senior role in which the person worked on the project for any significant length of time. For example, if an undergraduate student graduated, entered graduate school, and continued to work on the project, show that person as a graduate student, preferably explaining the change in involvement.

Describe how this person contributed to the project. If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name: Raquel Gardner

Project Role: PI

Researcher Identifier: unknown

Nearest person month worked: 15% effort over 12 months

Contribution to Project: PI, organizing protocols, hiring staff, setting up sub-contracts to OHSU, UCSF, UPenn, finalizing all aspects of protocol

Name: Yael Rozen Lang

Project Role: Data Scientist

Nearest person month worked: 40% effort over 9 months

Contribution to Project: Creates REDCap database, leads all data management and analysis.

Name: Mor Yerushalmi

Project Role: Sheba Research Coordinator

Nearest person month worked: 50% effort over 3 months

Contribution to Project: Leads Sheba Helsinki submission, creating case report form packet for all sites, creating REDCap database.

Name: Shlomit Pasternak

Project Role: Sheba Research Coordinator

Nearest person month worked: 40% effort over 3 months

Contribution to Project: Leads Sheba Helsinki and OHRO submission, creates study wide protocol and pdf case report forms.

Name: Noa Angel

Project role: Sheba Program Manager

Nearest person month worked: 20% effort over 2 months

Contribution to Project: Leads all sub-contracts, industry contracts, orders.

4. Changes/Problems: The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant

changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

a. Actual Problems or delays and actions to resolve them

Provide a description of current problems or issues that may impede performance or progress of this project along with proposed corrective action. Also describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

For an award that includes the recruitment of human subjects for clinical research or a clinical trial, discuss any problems or barriers encountered, if applicable, and what has been done to mitigate those issues. Discussion may highlight enrollment problems, retention problems, and actions taken to increase enrollment and/or improve retention.

We are experiencing some delays in launching the prospective cohort enrollment and the analysis of the banked samples, however, we continue to make steady forward progress towards both of these objectives. The final remaining step to be sorted out before cohort enrollment launch at the U.S. sites is to obtain final OHRO approval and to provide blood collection kits to the sites. The final step remaining before we begin analysis of existing samples is for Quanterix kits to be shipped to Les Shaw's lab and for ADNI-DOD samples to be shipped to WashU lab.

b. Anticipated Problems/Issues

Provide a description of anticipated problems or issues that have a potential to impede performance or progress. Also provide course of actions planned to mitigate problems or to take should the problem materialize.

Once we obtain OHRO approval and all sites have the blood collection kits in hand, then each site will be prepared to begin recruitment of patients. Production of the blood collection kits by NCRAD and/or Sheba could be delayed if any of the necessary materials are back-ordered. We were unable to order these too far in advance because some of the components have a limited shelf-life.

5. Special Reporting Requirements: N/A