

NAPA Research Progress Report

NAPA Advisory Council Meeting

Richard J. Hodes, M.D.
Chair, Federal Research Subcommittee

February 3, 2014

G8 UK
United Kingdom 2013



G8 Summit and Dementia Challenge

On January 15, 2014, NAPA Council Members Richard Hodes, George Vradenburg, and Harry Johns reported to the House Foreign Affairs Subcommittee on Africa, Global Health, Global Human Rights, and International Organizations on the December 11, 2013, G8 Dementia Summit in London.

NAPA Research Update From Recommendations to ACTION



NAPA Research Milestones – 2013 Genetics

- **Established** a consortium of genetics and genomics experts to execute a large scale sequencing project to identify AD risk and protective gene variants in subjects with late onset AD.
- **Initiated** development of a searchable, open access database to identify regions of the genome that contain novel targets.

database of **Genotypes and Phenotypes** (dbGaP)

<http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/about.cgi>

NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS)

<https://www.niagads.org/content/about-niagads>

Alzheimer's Disease Sequencing Project (ADSP) Background

- **Presidential Initiative:** February 7, 2012 to treat/prevent AD
 - NIA and NHGRI to develop and execute a large scale sequencing project
 - WGS - 582 subjects in 111 families and WES 5,000 cases and 5,000 controls
 - Identify AD risk and protective gene variants
- **Long-term Objective:** Facilitate identification of new pathways for therapeutic approaches and prevention
- **Support:** \$25M already committed to NHGRI's Large-Scale Sequencing Centers (LSSC) for genomic studies
- **Participants:** 2 NIA funded AD Genetics Consortia, 3 NHGRI Large Scale Sequencing Centers, NIH staff

ADSP – First Data Release

Family Based Study

Whole genome sequence data from 410 individuals in 89 families with multiple members affected with AD made available to qualified investigators on December 2, 2013.

ADSP - Future Activities

Data Release

- Complete WGS data (582 subjects in 111 families) - expected March 2014
- Whole exome sequence (WES) data (5,000 cases and 5,000 controls) and from 1,000 additional cases from families multiply affected by AD - expected summer 2014

U19: Cooperative agreement to support analysis of ADSP sequence data <http://grants.nih.gov/grants/guide/pa-files/PAR-12-183.html> to be funded spring 2014

Replication and Validation

- Acquire DNA from as many as 50,000 subjects for a replication study
- Conduct deep targeted re-sequencing and genotyping of candidate AD gene regions
- Conduct data analysis

NAPA Research Milestones - 2013

Other Updates

- **Completed development of and continued to populate** the International Alzheimer's Disease Research Portfolio (IADRP) with projects from additional funders. A partnership between NIA and the Alzheimer's Association.
<http://iadrp.nia.nih.gov/cadro-web/>
- **Convened the "Enabling Partnerships for Alzheimer's Disease Drug Development" advisory meeting** on April 30, 2013, focusing on facilitating public private partnerships (PPPs) for accelerating the development and testing of effective therapies for AD treatment and prevention.
<http://www.nia.nih.gov/research/blog/2013/06/enabling-partnerships-alzheimers-disease-drug-development-meeting-report>

Updates on NAPA Research Milestones - 2014

Drug Development

- Convene an advisory meeting to advance rational drug repositioning and combination therapy.
Considering this as part of the 2015 AD Summit.
- Establish agreements among stakeholders to expedite rigorous clinical testing of repurposed drugs.
Not yet initiated.
- Initiate efforts to identify, characterize, and complete early validation for at least 6 novel therapeutic targets for AD.
Several awards made in 2013 to accelerate these efforts.

Updates on NAPA Research Milestones - 2014

Biomarkers of Disease Progression

- Initiate synthesis and testing of novel PET ligands and develop and test novel CSF/blood biomarkers for assessment of disease related pathological burdens and initiate development of imaging and/or fluid biomarkers to demonstrate target engagement for novel therapeutic targets for AD. *Multiple studies initiated in 2013.*
- Begin launch of research programs to develop sensitive neuropsychological assessment measures to detect and track the earliest clinical manifestations of AD. *Not yet initiated.*
- Develop and test methods for the standardization of immunoassays, mass-spectrometry/single reaction monitoring, and the collection and analysis of MRI and PET neuroimaging data. *Ongoing efforts underway through ADNI and the Biomarkers Consortium.*

Updates on NAPA Research Milestones - 2014

Epidemiology

- Establish an expert panel of epidemiologists and clinical trialists to make recommendations for best practices in the use of existing epidemiology of dementia databases to individualize treatments in clinical trials on AD in heterogeneous populations.

Not planned for 2014.

- Initiate expansion of epidemiology of dementia cohorts to include subjects in midlife and use data generated to inform clinical trial design. *No new cohorts established.*

Updates on NAPA Research Milestones - 2014

Infrastructure

- Begin creation of translational centers for integration of multi-modal data analysis, mathematical modeling and empirical testing, and application of a systems biology/systems pharmacology approach to preclinical therapy development.
- Initiate creation of a National IRB.
- Establish a working group to identify standard outcome measures for data comparisons across a variety of clinical studies and begin initiation of clinical research studies using common standard outcome measures.

Updates on NAPA Research Milestones - 2014 Study Recruitment and Participation

- Develop references and tools to increase knowledge among research scientists of best practices for recruitment and retention of research participants. *Activities through inter-agency Recruiting Older Adults into Research (ROAR).*
- Establish a working group including clinical trial recruitment experts to dynamically evaluate and update the materials and information provided in the central resource. *Working group established and active. Have incorporated suggestions into ROAR effort.*
- Create a central repository of AD related registries and cohorts and increase awareness of large-scale registries that encompass the spectrum of the disease.
- Continue efforts to increase rates of enrollment and inclusion of underrepresented populations for AD clinical trials. *Activities through ROAR.*

New 2014 NIA Research Initiatives

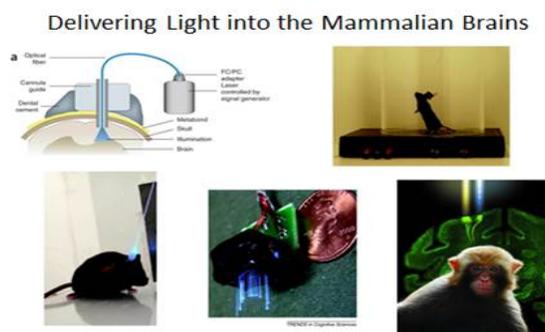
- RFA-AG-14-012: Human Cell Reprogramming for Functional Genetics of Alzheimer's Disease (R01)
- RFA-AG-14-002: Optogenetic Tools for the Study of Neural Systems in Aging and Alzheimer's Disease (R01)

Human Cell Reprogramming for Functional Genetics of Alzheimer's Disease (R01)

- Supports research to define the function of genes that have been implicated in causing or increasing the risk of Alzheimer's Disease using human neural cells derived from induced pluripotent stem cells.
- These studies may identify new cellular or molecular pathways underlying AD.

Optogenetic Tools for the Study of Neural Systems in Aging and Alzheimer's Disease (R01)

Supports applications of optogenetic tools for research on normal and/or pathological aging of neural systems as well as to encourage additional development of aging and Alzheimer's specific optogenetic tools.



2012-2013

**ALZHEIMER'S DISEASE
PROGRESS REPORT**

Seeking the Earliest Interventions

www.nia.nih.gov/alzheimers/progress-report

Meeting Announcement

INSTITUTE OF MEDICINE *Advising the nation • Improving health*
OF THE NATIONAL ACADEMIES

The Public Health Dimensions of Cognitive Aging Consensus Study

First Committee Meeting
February 3, 2014
National Academy of Sciences
Room 125
2101 Constitution Ave., N.W.
Washington, DC 20001

Study Sponsors

McKnight Brain Research Foundation
National Institute on Aging
National Institute of Neurological Disorders and Stroke
American Association of Retired Persons