NAPA Research Progress Report

NAPA Advisory Council Meeting

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

December 2, 2013

Predicted Mechanisms of LOAD GWAS
Alzheimer’s Disease Associated Genes

<table>
<thead>
<tr>
<th>Innate immune/brain inflammatory response</th>
<th>Endocytosis and cellular protein trafficking including APP trafficking</th>
<th>Lipid transport/metabolism</th>
<th>Synaptic transmission</th>
<th>Cytoskeletal function</th>
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</thead>
<tbody>
<tr>
<td>HLA-DRB5/HLA-DRB1/TREM2/CR1/CLU/MS4A4/MS4A6E/EPHA1/INPP5D/ABCA7</td>
<td>SORL1/PICALM/BIN1/CD2AP</td>
<td>APOE/CLU/ABCA7</td>
<td>PTK2B/MEF2C</td>
<td>CELF1/NME8/CASS4/FERMT2</td>
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*Nature Genetics (Oct. 27, 2013)*
2013 RFA: Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for AD

- Supports interdisciplinary and integrative research focused on identification and preclinical validation of novel targets for AD treatment and prevention
  - Encourages the pursuit of paradigm-shifting biological and therapeutic hypotheses and promotes the creation of new translational teams
  - Encourages the use of network-based approaches, such as systems biology and systems pharmacology to gain understanding of the molecular and physiological context within which potential therapeutic targets operate

2013 RFA: Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for AD

- **U01-A Systems Approach to Targeting Innate Immunity in Alzheimer’s** – Dr. Todd Golde, University of Florida, and Colleagues

- **U01-Pathway Discovery, Validation and Compound Identification for Alzheimer’s Disease** – Drs. Philip De Jager, Brigham and Women's Hospital, Broad Institute, Harvard University, Boston, and David Bennett, Rush University Medical School, Chicago

- **U01-Integrative Biology Approach to Complexity of Alzheimer’s Disease** – Dr. Eric Schadt of Icahn School of Medicine at Mount Sinai, New York City, and Team of investigators

2013 RFA: Alzheimer's Disease Prevention Trials

- Phase II or Phase III clinical trials testing pharmacological (small molecules and biologics) and non-pharmacological interventions, in cognitively normal individuals at-risk for AD (e.g., individuals at risk genetically, older adults positive for biomarker evidence of Alzheimer’s disease pathology) or in individuals with MCI using a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes.

2013 RFA: Alzheimer's Disease Prevention Trials*

- **UF1 - The Alzheimer's Prevention Initiative APOE4 Trial** – Drs. Eric Reiman and Pierre Tariot, Banner Alzheimer’s Institute, Phoenix, and Co-investigators

- **U01 – Stimulating the Innate Immune System to Prevent Alzheimer’s** – Dr. Ted Ashburn, Sanofi Aventis, Cambridge, Mass., in partnership with Baylor College of Medicine, Houston, Texas

Not supported from RFA, but part of FY 2013 AD Funds:

- **U01 -The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Trial** – Dr. Randall Bateman, Washington University, St. Louis, MO, and Co-investigators

2013 RFA: Alzheimer's Disease Phase I Clinical Trials

- Provide support for first-in-human studies for promising AD therapeutics.
- Evaluate the metabolic and pharmacological actions of drugs, including biologics in humans.

**UF1- Allopregnanolone Regenerative Therapeutic for MCI/Alzheimer’s: Dose Finding Phase 1** – Drs. Roberta Brinton and Lon Schneider, University of Southern California, Los Angeles

ALZHEIMER’S DISEASE-RELATED DEMENTIAS:
Research Challenges and Opportunities

Sponsored by the
National Institute of Neurological Disorders and Stroke
in cooperation with:
- National Institute on Aging
- Alliance for Aging Research, ACT-AD
- Alzheimer’s Association
- Association for Frontotemporal Degeneration
- USAgainst Alzheimer’s

www.ninds.nih.gov/ADRelatedDementias2013

CONFERENCE

• Goals
  – Each topic area presents rationale for prioritized research recommendations and timelines
  – Provoke discussion among group experts
  – Solicit feedback and opinions from audience

• Outcomes
  – 567 registrants: 322 in-person, > 200 on-line
  – Lively 2-day public session with many comments
    • Culminated with “open mike” and review of all suggested revisions
  – Closed session to plan post-conference work
EXECUTIVE SUMMARY - Overall

<table>
<thead>
<tr>
<th>TOPIC AREA</th>
<th>FOCUS AREA (number of prioritized research recommendations)</th>
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<tbody>
<tr>
<td>1. Multiple etiology dementias (MED)</td>
<td>Differential Diagnosis (3)</td>
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<tr>
<td>2. Health disparities (HD)</td>
<td>Recruitment (4)</td>
</tr>
<tr>
<td>3. Lewy body dementias (LBD)</td>
<td>1. Establish longitudinal cohorts with common measures, culminating in autopsy studies (2)</td>
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<tr>
<td>4. Frontotemporal dementia and other tauopathies (FTD)</td>
<td>Basic Science: Pathogenesis and Toxicity (4)</td>
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<td>5. Vascular contributions to ADRD - focus on small vessel disease and AD/vascular interactions (VAS)</td>
<td>Basic Mechanisms and Experimental Models (3)</td>
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EXECUTIVE SUMMARY – Overlap

- Although ordering of priorities and timelines differed, several recs applied across ADRD (and AD)
  - Fundamental research to fill critical knowledge gaps
  - Training and education to ensure durable progress
  - Improved diagnostics
  - Optimized repositories
  - All recommendations within HD
  - Culmination of research in effective interventions
Alzheimer's Disease Summit: The Path to 2025

November 6 - 7, 2013
The New York Academy of Sciences

Presented by The New York Academy of Sciences, National Institute on Aging/NIH and the Global CEO Initiative on Alzheimer's Disease

Alzheimer's Disease Summit: The Path to 2025

Primary Goal: To convene leading industry, academic, and government stakeholders in discussions regarding how to prevent and effectively treat Alzheimer's by 2025:

- Coordinating with governmental efforts to build research resources
- Reengineering our current drug development and evaluation systems
- Identifying innovative technologies and financing models

Outcome: To comprise a research agenda that will delineate the pathways needed to effectively treat and prevent Alzheimer's disease by 2025.

www.nyas.org/pathto2025
UK Hosts the First G8 Dementia Summit on December 11, 2013

Host: The Right Honorable Jeremy Hunt MP

Participating Countries:
Canada
France
Germany
Italy
Japan
Russia
USA
United Kingdom

https://www.gov.uk/government/news/uk-to-host-g8-dementia-summit

SAVE THE DATE

Alzheimer’s Disease Research Summit 2015

February 9-11, 2015
National Institutes of Health
U.S. Department of Health & Human Services
Bethesda, MD