NAPA Research Progress Report

NAPA Advisory Council Meeting

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April 29, 2014

2015 Summit Plans

• February 9th-11th, 2015
  — February 9th-10th: Alzheimer’s Disease Research Summit
  — February 11th: G8 Summit Legacy Meeting on international research coordination – treatment, cure, and prevention

• Draft agenda reflects input from the Trans-NIH AD Working Group and National Advisory Council on Aging
Draft Outline for Summit Presentations

- Introductory Remarks
- NAPA Research Milestones: Process and Progress
- Plenary Lecture(s): Socioeconomic Burden of AD: Update on National and International Trends
- Session I: Interdisciplinary Research to Understand the Heterogeneity and Multifactorial Etiology of AD
- Session II: Transforming AD Therapy Development: from Targets to Trials
- Session III: New Strategies for Prevention
- Session IV: Innovating disease monitoring, assessment and care
- Session V: Partnerships Enabling Open Innovation
- Session VI: Empowering Patients, Engaging Citizens

Plans for New Monies

- Of the approximately $100 million in new funds for FY15 for AD, a strategy will be applied to provide stable availability of funds for new awards across future years:
  - $80 million will be used to fully fund some projects (e.g., $4 million total might be set aside now for a project that costs $1 million/year over 4 years)
  - $20 million will be used to fund the first year for other projects – this is the typical approach that the NIA uses; subsequent year funding would be from the base
FY2014 NIA Alzheimer’s 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)
- PAR-12-183: National Institute on Aging Analysis of Alzheimer's Disease Genome Sequencing Project Data [U19]

Funding Approach for FY15

- FY15 initiatives will be considered during the May meeting of the National Advisory Council on Aging
- A process is being established to map individual projects to NAPA goals on a regular basis
- Initiatives can be generally mapped to NAPA goals after the May Council meeting
Accelerating Medicines Partnership

Alzheimer's Disease Program

Why AMP? Why now?

Developing effective new medicines takes too long, costs too much and fails too often.
AMP Pilots:
Alzheimer’s disease
Type 2 diabetes
Rheumatoid arthritis/systemic lupus erythematosus

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Alzheimer’s Disease – AMP Proposal Development Group

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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<tbody>
<tr>
<td><strong>Co-Chairs</strong></td>
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<tr>
<td>Steve Paul</td>
<td>Weill Cornell Medical College</td>
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<tr>
<td>Mike Hutton</td>
<td>Lilly</td>
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<td><strong>Industry</strong></td>
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<tr>
<td>Charlie Albright</td>
<td>BMS</td>
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<td>Richard Hargreaves</td>
<td>Merck</td>
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<td>Holger Rosenbrook</td>
<td>Boerhinger-Ingelheim</td>
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<td>Leslie Shinobu</td>
<td>Takeda</td>
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<td>Mike Decker</td>
<td>AbbVie</td>
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<td>Xiaoming Guan</td>
<td>GSK</td>
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<td>Tim Harris</td>
<td>Biogen Idec</td>
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<td><strong>Academia, Government, &amp; Non-profit</strong></td>
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<tr>
<td>Randy Bateman</td>
<td>Washington Univ St Louis</td>
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<tr>
<td>Todd Golde</td>
<td>Univ of Florida</td>
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<tr>
<td>Eric Karran</td>
<td>Alzheimer’s Research UK</td>
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<td>Eric Reiman</td>
<td>Banner Alzheimer’s Institute</td>
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<tr>
<td>Neil Buckholtz</td>
<td>NIH/NIA</td>
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<tr>
<td>Dave Holtzman</td>
<td>Washington Univ St. Louis</td>
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Original Research Proposal for Alzheimer’s Disease

Key scientific elements of proposed research

A. Identify biomarkers correlated with therapeutic benefit
- Embed exploratory biomarkers into upcoming Phase 3 clinical trials to identify those which predict clinical benefit
  - Study includes supplemental biomarker assessments of 1000 patients in 5 different trials across 100 sites
  - Specific assessments to include: Expanded MRI battery, FDG-PET, Abeta/Tau imaging, CSF markers and others
  - Includes collaboration with the FDA to define what is needed to ultimately qualify biomarkers as surrogate endpoints in registration trials
  - Timeline is 5 years

B. Identify & validate new targets in human brain tissue
- Integrated systems analysis in human brain tissue to identify networks and validate targets relevant in AD
  - Conduct RNA seq / GWAS studies in 3000 existing brain samples using validated methodologies (2000 AD, 1000 Control)
  - Construction of ordered networks linked to disease is expected to identify novel targets and provide orthogonal target validation with human genetics (GWAS and deep sequencing)
  - Timeline is 3 years

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

Identification and Validation of Novel Therapeutic Targets for Alzheimer’s Disease,
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.


### Summary of recently announced NIH initiatives:
Identifying biomarkers correlated with therapeutic benefit

<table>
<thead>
<tr>
<th>Proposal</th>
<th>Description</th>
<th>Principal investigator</th>
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<tbody>
<tr>
<td><strong>Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Trial</strong></td>
<td>Phase III study to assess the safety, tolerability, and biomarker efficacy of gantenerumab and solanezumab in mutation carriers</td>
<td>Randall J. Bateman, WUSL</td>
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<td><strong>The Alzheimer’s Prevention Initiative APOE4 Trial</strong></td>
<td>Testing an anti-amyloid drug (TBD) in cognitively normal older volunteers who are at increased risk of developing late-onset Alzheimer’s (APOE4)</td>
<td>Eric Reiman, BANNER; Pierre Tariot, BANNER</td>
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<tr>
<td><strong>Alzheimer’s Disease Cooperative Study Anti-Amyloid Treatment in Asymptomatic AD Trial (A4)</strong></td>
<td>Secondary prevention trial of MAb in clinically normal older people with biomarker evidence of brain amyloid</td>
<td>Reisa Sperling, Harvard; Paul Aisen, UCSD</td>
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[Click links to view full project descriptions](#)
NIH-funded Phase II/III studies in preclinical, at-risk patients

**Source**
- API APOE4
  - CSF AB42
  - p-tau
  - t-tau
  - Plasma A81-40
  - Plasma A8x-40
  - Plasma A81-42
  - Plasma A8x-42
- DIAN
  - CSF tau
  - CSFAB42
  - CSFAB40
  - CSF p-tau
  - BACE
- A4 prevention
  - CSF AB1-42
  - CSF tau
  - CSF p-tau

**Fluid**
- Imaging
  - MRI
  - Axial T2 Stair
  - Gradient Echo
  - FDG PET/AB PET
  - Axial T2 FLAIR
  - MPRAGE/IR/SPGR
  - tDMR EPI BOLD
  - Axial DTI
  - Axial T2 TSE
  - Fluorotetramol PET

**Subjects**
- 650
- 155
- 1000

Each trial collects CSF & plasma; Access to samples would need to be defined

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**AMP Project A**

- Supplement the biomarker panels already included in these three NIH-funded Phase II/III registration trials in presymptomatic Alzheimer’s through the addition of tau PET imaging, EEG measures and novel fluid biomarkers.

  ➢ AMP will support appropriate CSF and plasma sampling and storage as necessary to ensure that the full range of future analytes can be measured including protein and miRNA biomarkers.

  ➢ The identity of the specific analytes will therefore be based on progress in the field over the next 5 years; however, output from the ADNI proteomics project among other large scale fluid biomarker programs will be available in this timeframe.
Diagnosing AD: Present and Future

MRI—structure  Tau  Amyloid

Alzheimer’s disease

Normal

Summary of recently announced NIH initiatives:
Identifying & validating new targets in human brain tissue

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<tr>
<th>Proposal</th>
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</table>
| **Pathway Discovery, Validation and Compound Identification for Alzheimer’s Disease** | - Characterize and validate complex molecular networks & candidate genes that influence susceptibility to AD  
  - Analyze rich clinical, pathological, genomic and other large-scale molecular data collected from brain tissue from over 1,000 subjects | - Philip De Jager, BROAD  
  - David Bennett, RUSH |
| **Integrative Biology Approach to Complexity of Alzheimer’s Disease** | - Construct biological network models with large-scale molecular, cellular and clinical data (incl. human cells) | - Eric Schadt, MT SINAI |
| **Systems Approach to Targeting Innate Immunity in Alzheimer’s** | - Identify and characterize novel therapeutic targets within the innate immune system using data from Alzheimer’s patients and Alzheimer’s mouse models | - Todd Golde, U Florida  
  - Nathan Price, Seattle  
  - Nulfer Ertken-Taner, Mayo |

Click links to view full project descriptions

AMP will support enabling effective data integration across these three NIH-funded studies
AMP Project B

- Expand the application of integrated network analysis (both RNA and proteomic studies) in human AD brain samples to identify biologic nodes and networks that are linked to the development or progression of AD.

- Plan to work with Sage Bionetworks to create standardized open-source data structures and formats to aid the accessibility and ease of analysis of biological data in a manner not currently practiced in the AD field. SAGE will provide coordinated and centralized enablement of the data components for public use.

Projected AMP funding contributions

<table>
<thead>
<tr>
<th>Disease area</th>
<th>Total project funding ($M)</th>
<th>Total NIH funding ($M)</th>
<th>Total industry funding ($M)</th>
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<tr>
<td>AD</td>
<td>135</td>
<td>67.6</td>
<td>67.4</td>
</tr>
<tr>
<td>T2D</td>
<td>58.4</td>
<td>30.4</td>
<td>28.0</td>
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<tr>
<td>RA/SLE</td>
<td>41.6</td>
<td>20.9</td>
<td>20.7</td>
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<tr>
<td>Total</td>
<td>235</td>
<td>118.9</td>
<td>116.1</td>
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Industry is also providing AMP with additional in-kind contributions, e.g., clinical trials, drug, tracer, databases, etc.