Alzheimer’s Disease: Research Challenges and Opportunities

104th Meeting of the Advisory Committee to the Director
National Institutes of Health
NIH Campus, Bethesda

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June 15, 2012
Prevalence of Probable Alzheimer’s Disease

Number of Persons with AD in Millions

Percent of Persons with AD by Age


Possible Environmental and Lifestyle Factors Affecting Alzheimer’s Disease

- Age
- Head Injury
- High Blood Pressure
- Cholesterol
- Homocysteine
- Diabetes
- Education/Brain Reserve/Occupation
- Exercise
- Social Contacts
Alzheimer’s Disease Gene Discovery

1991
- APOEε4
- APP*
- PS1*
- PS2*

1995
- PS1*
- PS2*

1996
- Transgenic Mouse models

2005
- First published GWAS

2009
- PICALM*
-CLU*
-CR1*
-GWAS

2010
- BIN 1
  Five additional genes* discovered by GWAS

2012

* Early onset Alzheimer’s Disease- family based studies
* Late onset Alzheimer’s Disease- case control studies

Range needed to identify genes: 3,000 – 27,000 cases and 11,000 – 41,000 controls
Neurofibrillary Tangles

Senile Plaques
Progressive spread of tauopathy in NT mice with antibody AT8
Tau Pathology Spread in Hippocampus

Entorhinal Cortex transgene-expressing neurons to neurons without detectable transgene expression

First to Entorhinal Cortex neighboring cells

Migration to neurons downstream in the synaptic circuit

Dentate Gyrus

Cornu Ammonis – all 4 fields

Cingulate Cortex
ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models

Bexarotene treatment of β-amyloid transgenic mice

- Decrease in plaques
  - Cortex
    - Plaque number per 10 μm section
    - Vehicle 3 day 7 day 14 day
  - Hippocampus
    - Plaque number per 10 μm section
    - Vehicle 3 day 7 day 14 day

- Improved memory
  - Time spent in the NW quadrant (s)
  - NonTg Veh APP/PS1 Veh APP/PS1 Bex

Treated for 20 days

Imaging Amyloid Plaques in Living People

Alzheimer’s Disease

Mild Cognitive Impairment

Normal

Wolk et al. Annals of Neurology 2009
Amyloid Plaques Precede Memory Problems

- Memory Problems 4 Years Later
- Stable Memory

Baltimore Longitudinal Study of Aging
AD Progression: ADNI Model

New Diagnostic Guidelines for Alzheimer’s Disease

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on workgroups on diagnostic guidelines for Alzheimer's disease.


Alzheimer’s Disease Research Summit 2012: Path to Treatment and Prevention

May 14-15, 2012
National Institutes of Health
U.S. Department of Health & Human Services
Bethesda, MD

http://www.nia.nih.gov/newsroom/alzheimers-disease-research-summit-2012-recommendations
Approximately 500 attended both days
Almost 500 watched nationally and internationally by webcast
Representatives from 38 states and 8 countries attended
HHS Secretary Kathleen Sebelius presented the National Plan and NIH Director, Dr. Francis Collins announced two AD Clinical Trials
Summit webcast is archived at: http://videocast.nih.gov
Alzheimer’s Disease Research Summit
Path to Treatment and Prevention

• Overarching issues transcended many of the sessions:
  – Heterogeneity of the disease
  – New research paradigms, e.g., systems biology needed
  – Rapid and extensive data/specimen sharing
  – Multidisciplinary translational teams
  – Strategies to overcome IP barriers
  – Public-private partnerships
  – National IRB

http://www.nia.nih.gov/newsroom/alzheimers-disease-research-summit-2012-recommendations
Alzheimer’s Disease Research Summit Recommendations

- **Session 1**: Interdisciplinary Approach to Discovering and Validating the Next Generation of Therapeutic Targets for AD

- **Session 2**: Challenges in Preclinical Therapy Development

- **Session 3**: Whom to Treat, When to Treat, and What Outcomes to Measure

- **Session 4**: Drug Repurposing and Combination Therapy

- **Session 5**: Nonpharmacological Interventions

- **Session 6**: New Models of Public Private Partnerships

- [http://www.nia.nih.gov/newsroom/announcements/2012/05/alzheimers-disease-research-summit-offers-research-recommendations](http://www.nia.nih.gov/newsroom/announcements/2012/05/alzheimers-disease-research-summit-offers-research-recommendations)
Alzheimer’s Disease Research Inventory

• Information about Alzheimer’s disease research available to the public online: http://www.nia.nih.gov/research/dn/international-alzheimers-disease-research-portfolio

• NIA has posted a preliminary list of projects coded using the Common Alzheimer’s Disease Research Ontology developed jointly by NIA and the Alzheimer’s Association

• Other funding organizations are invited to join the effort and list their research projects
Alzheimer’s Disease Projects Funded by FY 2012 NIH Additional $50 million

On February 7, 2012, Secretary of Health and Human Services Kathleen Sebelius announced that $50 million would be directed immediately to boost Alzheimer’s research in FY2012 in response to President Obama signing the National Alzheimer's Project Act.

The following research projects will be funded:

• AD genome sequencing by NHGRI Genome Centers

• Use of new induced pluripotent stem cell methods to obtain insights into the cellular processes of Alzheimer’s

• Small Business Alzheimer's Disease Research (STTR) R41/R42 -Phase I, Phase II, and Fast-Track / Small Business Innovation Research (SBIR) R43/R44 Grant - Phase I, Phase II, and Fast-Track

• Two AD Clinical Trials - one treatment and one prevention
* Early onset Alzheimer’s Disease- family based studies
* Late onset Alzheimer’s Disease- case control studies

Range needed to identify genes: 3,000 – 27,000 cases and 11,000 – 41,000 controls
A General Approach for the Use of iPSCs to Model AD

Israel and Goldstein, Genome Med, 3:49, 2011
Pilot Trial of Intranasal Insulin for Alzheimer’s and MCI

- **Pilot**: 104 adults with MCI and mild to moderate Alzheimer’s; placebo, 20 IU insulin, 40 IU insulin for 4 months, administered with nasal drug delivery device

- **Results**:
  - improved delayed memory in 20 IU group compared with placebo
  - preserved general cognition, activities of daily living for younger participants in both insulin groups
  - caregivers for both insulin groups rated participant functional status higher
  - changes in some biomarkers (Aβ42 and tau to Aβ42 ratio) associated with changes in memory and function

*Suzanne Craft et al, Arch Neurol 2012 January; 69(1): 29-38*
Age 35-39 Years

Gene Carriers

Non-Carriers

Age 25-29 Years

Colombian Kindred
- N = 5000 living individuals from ~ 25 families
- 1000 with the E280A (Glu280Ala) Presinilin1 mutation
- Autosomal dominant, 100% penetrance
- Median age of MCI = 44 years, dementia = 49 years

Reiman, Fleisher and colleagues – not for public distribution
Goal 1: Prevent and Effectively Treat Alzheimer’s Disease by 2025

Goal 2: Enhance Care Quality and Efficiency

Goal 3: Expand Supports for People with Alzheimer’s Disease and Their Families

Goal 4: Enhance Public Awareness and Engagement

Goal 5: Improve Data to Track Progress
Session 1: Interdisciplinary Approach to Discovering and Validating Next Generation Therapeutic Targets

- Understand complex pathobiology
- Systems-level understanding
- Genetic info to inform mechanistic insights
- New experimental models
- New *in vivo* imaging agents
- Robust biomarkers, large cohorts
- Peripheral biochemical changes
- Rapid sharing of new data/collaborative efforts
- Maximize existing infrastructure
- New translational teams
Session 2: Challenges in Preclinical Therapy Development

- Create infrastructure and resources to increase likelihood that preclinical therapeutic development will be successful
  - Expert advisory committees
  - Network of AD preclinical therapy centers
  - Open-access resource for negative data
- Develop broad capabilities in quantitative and systems pharmacology
- Increase predictive power in animal models
  - Standardized processes for animal models
  - Align features of AD animal models with clinical disease-biomarkers
  - Rigor and reporting of positive and negative data
- Expedited review track for applications
Session 3: Whom to Treat, When to Treat, and What Outcomes to Measure

- Initiate treatment trials in asymptomatic, at-risk individuals using biomarkers
- Collect DNA and biomarkers
- Expand large-scale registries, pop-based
- Neuropsychological/behavioral characterization of early changes
- Optimize biomarkers, standardization
- Treatment for symptomatic patients
- Stratify and individualize treatments
- Infrastructure for prevention initiatives
Session 4: Drug Repurposing and Combination Therapy

- Expand libraries of drugs, tissues for different stages of AD
- Maintain rigor in repurposed drug development
- Combination therapy may be necessary
- Evaluate drugs with multiple targets
- Develop translational groups across institutions
Session 5: Non-pharmacological Interventions

- Epidemiological data with mechanisms
- Identify molecular mechanisms, systems approach
- Rigorous clinical trials in asymptomatic and impaired subjects to establish effectiveness
- Combine non-pharmacological with pharmacological
- Standardize outcome measures
- Science of behavioral change
- Invest in technologies
Session 6: New Models of Public Private Partnerships

- Promote partnerships across all sectors
- Increase awareness of the value
- Enable partnerships for
  - Data sharing
  - Sharing tools for translational research
- Expand precompetitive space using new models
- Develop National IRB accessible to both public and private organizations