ADNI Private Partner Scientific Board (PPSB) Perspectives on WW-ADNI

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For the ADNI PPSB

WW ADNI Meeting

15 July, 2011

Paris, France

Acknowledgements to

Bill Potter, Eric Siemers, Judy Suiciak, Holly Soares, Mark Schmidt, Maria Carrillo, Mike Weiner, Pat Cole

Overview

- Role of Private Partner Scientific Board (PPSB), formerly Industry Scientific Advisory Board (ISAB)

- Industry Perspective on Issues Facing AD Drug Development

- PPSB Perspective of benefits participating in ADNI I and ADNI II

- WW-ADNI & PPSB: Potential for Collaboration?

ADNI
PPSB

ADNI Public-Private Partnership Structure

Private/Philanthropic

+

Public

Judy Siuciak, Erika Tavers
Alison Drone

Neil Buckholtz
John Hsiao

ADNI Executive Steering Committee

PET Core: Berkeley: Jagust	**MRI Core:** Mayo: Jack	**Clinical Core:** UCSD: Aisen Mayo: Peterson

PI: Mike Weiner
Administrative Core: UCSF

Biomarkers Core:
UPenn: Trojanowski/ Shaw

Publications Core:
BostonU: Green

Informatics Core:
 UCLA: Toga

Biostatistics Core:
UCD: Beckett

Pathology Core:
 WashU: Morris

57 Clinical Sites: ADNI PIs and Cores

What does the PPSB do?

- Charter/Scope:
  - Collaborate with ADNI2 Steering & Executive Committees & Cores in the conduct of ADNI2 and creating value for the PPSB and community in accelerating drug development

- Key Goals
  - In pre-competitive space evaluate needs/gaps and recommend projects or analyses that could accelerate drug development
  - Convene Work Streams or Working Groups to tackle identified gaps / improvements
    - Current WGs include Database WG, PET Endpoint WG, Aβ as a biomarker WG, ADAS-Cog Plus WG (Optimize ADAS-Cog)

- **Database Working Group**:
  - Work collaboratively with the ADNI Biostatistics and Informatics Cores to develop a strategy to improve the database usability for all ADNI data beneficiaries.
  - Focused on the description, standardization and organization of available clinical and biomarker data from ADNI to improve data access, facilitate data integration and aid analysis.
  - Eg: WG will help beta test new LONI interface before deployment

- **PET Imaging Endpoints Working Group**:
  - Support the ADNI mission to validate imaging biomarkers.
  - Focused on the 'technical' validation of PET for use in clinical trials as treatment endpoints.

- **Aβ as a Biomarker Working Group**:
  - Established to identify and characterize underlying factors that contribute to intra-subject variability in CSF Aβ levels with multiple draws over a period of 24-48 hours. In 2010, collected multiple placebo data sets for analysis.

Major Hurdles Facing AD Drug Development

- Aβ targeting therapeutics have thus far failed to show effect resulting in discontinuation of programs
    - Target? Therapy mechanism of action?
    - Clinical trial design? Outcome measures?
    - Stage of disease (Mild to Moderate vs early/prodromal AD)?

- Clinical trial design for disease modifying therapeutics is difficult
    - Demonstrating clinical benefit in AD requires lengthy trials making drug development costly
    - Lack of sensitive and unbiased methods to detect disease progression necessitates high front-end investments
        - i.e., very large clinical studies during early stages of development
    - Need for biomarker evidence that therapy is altering the underlying pathophysiology of AD
        - Variability of assay or image analysis methology
        - Which to select, what about standardization?

Modified from Mike Weiner

- A disease modification therapy (that works)
- Optimization of clinical trial programs to accelerate drug development
  - Sensitive tools to measure progression
  - Establish biomarkers as surrogates of clinical endpoints
  - Identify response biomarkers
  - Standardization of assays to measure biomarkers (biochemical & imaging)
- Detect AD pathology in the brain in people without symptoms or complaints
- Ability to measure change of AD in the brain

ADNI Goals

ADNI was initiated to improve clinical trials for disease modifying treatments through:

- Validation of biomarkers:
    - as measures of change
    - as diagnostics or predictors (symptomatic and pre-symptomatic)

- Optimizing and standardizing biomarker methods

- Principle of data sharing beyond participating PIs, and ADNI funders

What has ADNI accomplished?

- Data Sharing:
  - Patient level de-identified baseline and longitudinal data made publically available for data mining, innovation and discovery
  - Raw and transformed data available
- Standardization of sample/data collection
  - Biomarkers: structural MRI, FDG PET, CSF Abeta/Tau methodology at 57 sites in US and Canada
  - Clinical outcome measures
- Elucidation of biomarker signatures and predictors for AD
- Numerous manuscripts, abstracts, presentations

Modified from Mike Weiner

- Biomarker baseline covariates improve statistical power of clinical/cognitive outcomes

  – Suggesting biomarkers decrease clinical trial costs by decreasing sample size, study length, and improving power to detect treatment effects.

  – Structural MRI and FDG PET show significantly greater statistical power than clinical/cognitive measures to detect rates of change in all subjects

- Correlations

  – MRI and PET significantly correlate with clinical/cognitive measures.

  – Baseline amyloid PET correlates with CSF Aβ confirming earlier reports with larger sample sizes

- Predictors for progression (from MCI to AD, for Normal Controls)

  – 15%/yr amnestic MCI progression rate and baseline MRI, PET and CSF ABeta/Tau data predicts MCI subjects that will progress to dementia.

  – Baseline amyloid PET predicts cognitive decline in controls and MCI suggesting utility as early AD tool.

  – Healthy cognitively normal controls with low CSF Ab have 2X greater rate of brain atrophy compared to controls with high CSF Ab. Data suggests biomarker measures may be earliest indicators of patients at risk.

Examples of Collaborations

- PPSB collaborations with ADNI cores in discussion or ongoing

- Biomarkers Consortium ADNI Plasma Proteomics Project data uploaded to ADNI website (November 2010), manuscript submitted (Hu et al):

  - Identification of plasma biomarker panel for diagnosis etc.

- Biomarkers Consortium ADNI CSF biomarker project ongoing

  - Identification of CSF biomarkers from list of candidates for diagnosis and progression

Unexpected ADNI Benefits….

- Understanding shifts in AD disease progression and placebo response over time.

    – ADNI data being used in modeling efforts to understand how slope changes today compare to those obtained in clinical trials completed 5-15 years ago. Item level data currently being made available with major support from industry and foundations

- Regulatory attention

    – ADNI methods are recognized and are being used in current FDA and EMA approved phase 2 & 3 AD trials

    – Progress toward regulatory acceptance of biomarkers as patient selection tools, evidence of pharmacological activity and as weight of evidence to support disease modification

Unexpected ADNI Benefits…cont...

- Engagement of the Global community…
  - ADNI-like studies now underway in Australia, Japan, China and Europe.
  - Meeting on worldwide standardization of Aβ and Tau assays scheduled for this July at ICAD
  - Establishing a world-wide network for clinical AD studies and treatment trials

- Sense of shared responsibility in understanding AD etiology, improving clinical trial methodology and helping patients.
  - Unprecedented level of cooperation and engagement amongst industry, private partners, and academic community who have been historically fierce competitors.

Emerging Biochemical & Disease Timeline

Future Direction
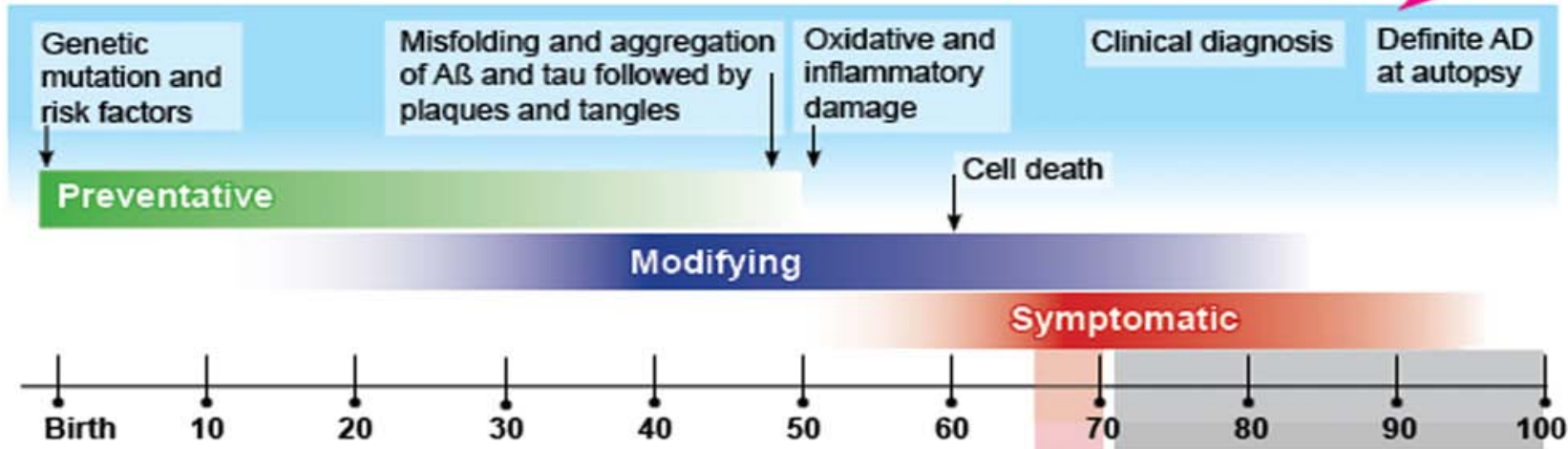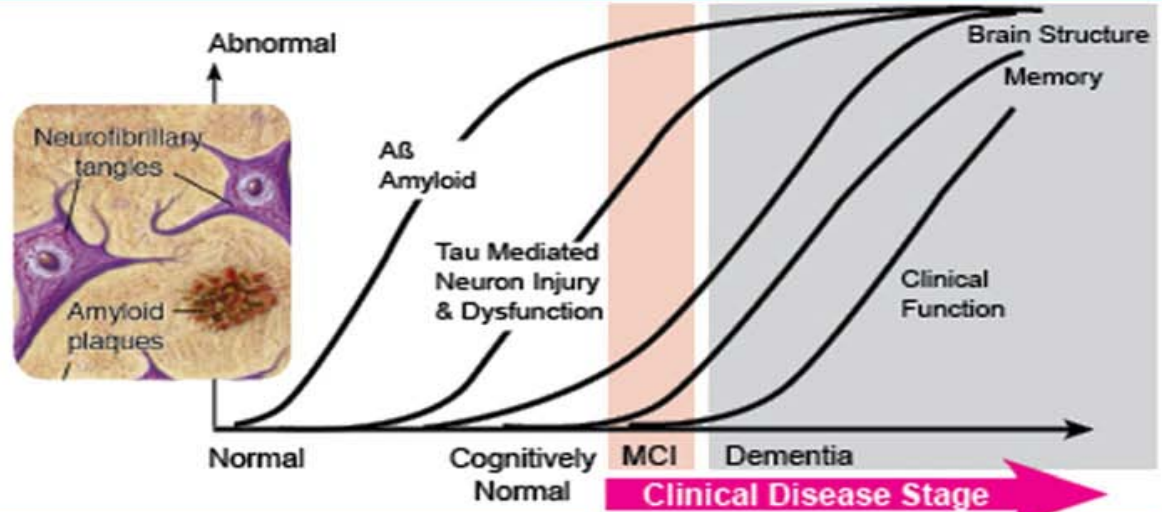
- ADNI GO & ADNI 2
  - Greater understanding of Alzheimer's disease earlier in the continuum
- Treatment earlier in disease continuum: Parallel thinking of the field and Industry
  - Dubois et al 2007 & Albert et al 2011 / Sperling et al 2011
  - BMS & Roche trials in early AD/mild AD
- Individual patient vs group prognosis
  - Utility in clinical practice and for enrollment in pre-symptomatic trials, we need to move toward understanding disease pathology pattern at individual patient level

Remaining Gaps

Drug Development Tools:

- Qualify tools for early diagnosis and drive standardization to level required in clinical studies for registration

- Lack of understanding around relevant clinical scales to monitor disease progression in non-demented early AD subjects.

Biomarkers:

- Alignment with FDA & CHMP around criteria for qualifying biomarkers for clinical use and suitable clinical trial design for early AD studies

- Lack of widespread acceptance in the field for implementation of CSF and imaging biomarkers as diagnostic/cohort enrichment tools to identify early AD

- Lack of widespread implementation of an F18 amyloid PET ligand at ADNI sites in preparation for use as a patient selection/ treatment monitoring tool.

Others:

- Address emerging safety issues: inclusion of MRI FLAIR & GRE/T2*

- Availability of a common data base (& data bank for fluid & DNA) to allow for head to head comparison of analytical methods

Modified from Bill Potter

PPSB Perspective on WW-ADNI

ADNI
PPSB

Congratulations and Applause to:

- Individual country for initiating efforts
- Alzheimer's Association's efforts to unify and harmonize the different ADNIs

We want to collaborate! How can we help?

- Share ideas and proposals for analyses or data collection: PPSB has drug development perspective
- Institute more links through teleconferences?
- Wider data sharing?

Questions? Thoughts?