ADNI Experience on Developing Biomarker Tools as Example of An Approach to Catalyzing Dry AMD Drug Development

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Disclosures

- Former employee of Lilly and Merck Research Laboratories

- Consulting within last 24 months:, Amgen, Astra-Zeneca,, EnVivo, Index Ventures, Ironwood, Lilly, Neurotrope, Taisho, Takeda, Theravance,

Factors Supporting Drug Development: Argument For ADNI

The case for investing in novel drugs for conditions such as Alzheimer's (and Dry AMD) requires advances across the discovery and development continuum:

- Better understanding of disease pathogenesis/pathophysiology
- **Better validation of drug targets**
- **Improvements in translational tools and methodologies**

What is a Target?

- **Any molecular or structural site of an intervention whether drug, electrical current or whatever**

- In the Clinical Realm:

  Symptom domain associated or not with a specific diagnosis (appropriate for many syndromal diagnoses but perhaps not for AMD)

What is Target Validation

- **Traditionally,** taking doses into humans through Phase 2 based on preclinical exposure/function curves
- **Too often**, progressing to Phase 3 with flawed Phase 2 data (NK1) or unclear data on brain effects (Dimebon)

For Drug Development: Degree to Which Evidence Supports Hypothesis that Efficacy Can be Achieved through a Given Target

- **Includes Body of Evidence**
- **Process of Gathering that Evidence**

Few Targets Validated or Rejected*: Thus, No Clear Basis for Business to Estimate Probability of Success

- **>75 Potential Antidepressant Targets**
  - **3 Validated and 3 Rejected**
- **> 50 Psychosis/Cognition in SCZ Targets**
  - **1 Validated and 3 Rejected (by Merck)**

- **>150 Targets for Alzheimer's Disease**
  - 1 Validated and ? 1 (γ-secretase) Rejected

*Taken from Adis R & D Database Classification of Classes of Compounds that have at least Entered Phase I

Elements to Consider…

- Neuroscience & Genetics to Identify Targets Related to Etiology and Pathophysiology
- Acute Molecular and Downstream Functional Effects at Targets in Preclinical Models and Humans Subjects
- **Disciplines and Time Required to Mature Markers of Disease State and Drug Effects to Apply to Individuals in Regulatory Standard Trials**

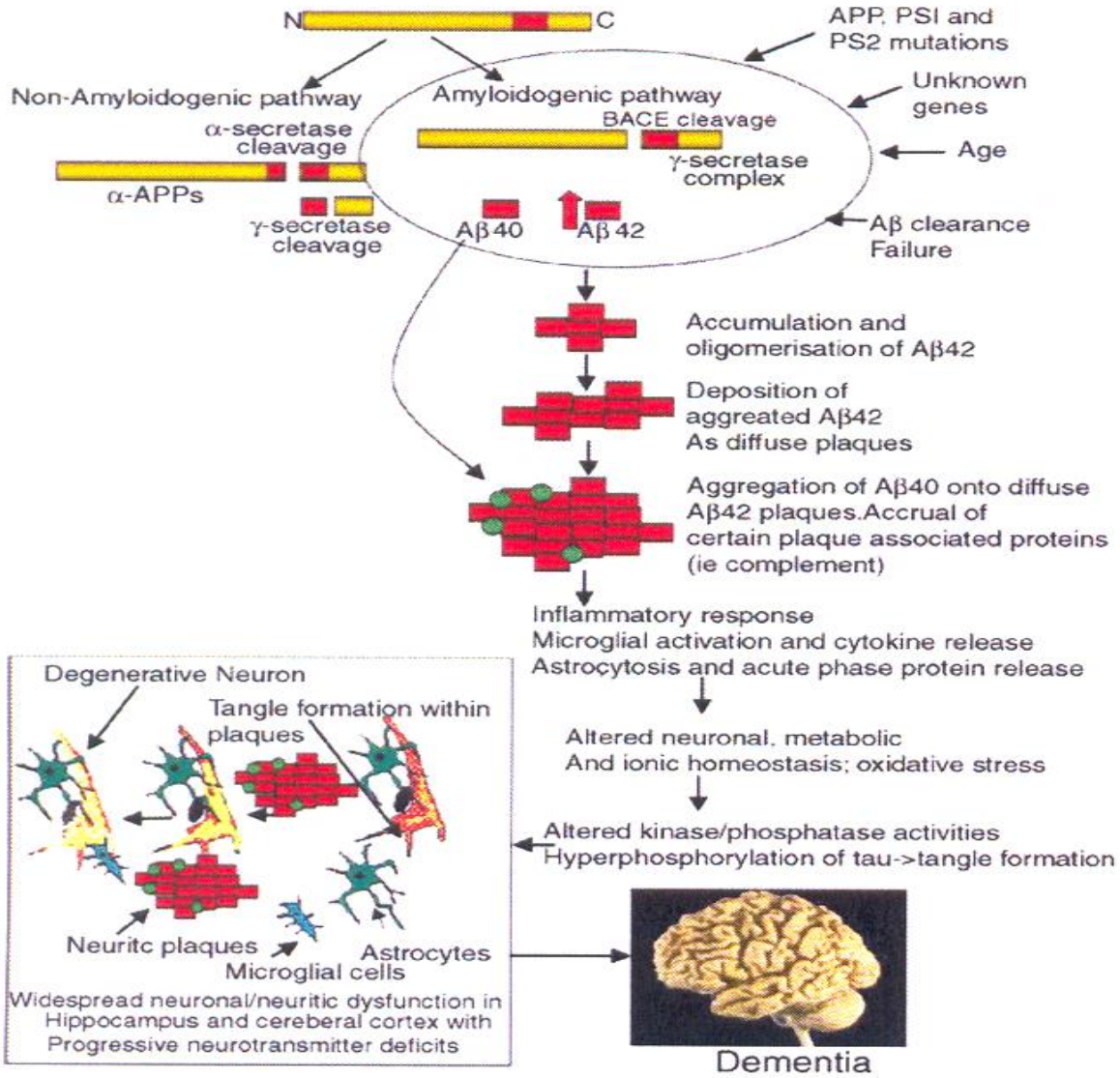
Therefore: A Collaborative Pre-Competitive Effort

- No single organization or laboratory can prioritize, align and execute studies needed to integrate levels of enquiry
- Biological expertise not enough: physics, mathematics, informatics, engineering….
- **Bring together all interested stakeholders to focus on a question to advance treatment -- ADNI Model**

Components to be Aligned for Risk Sharing

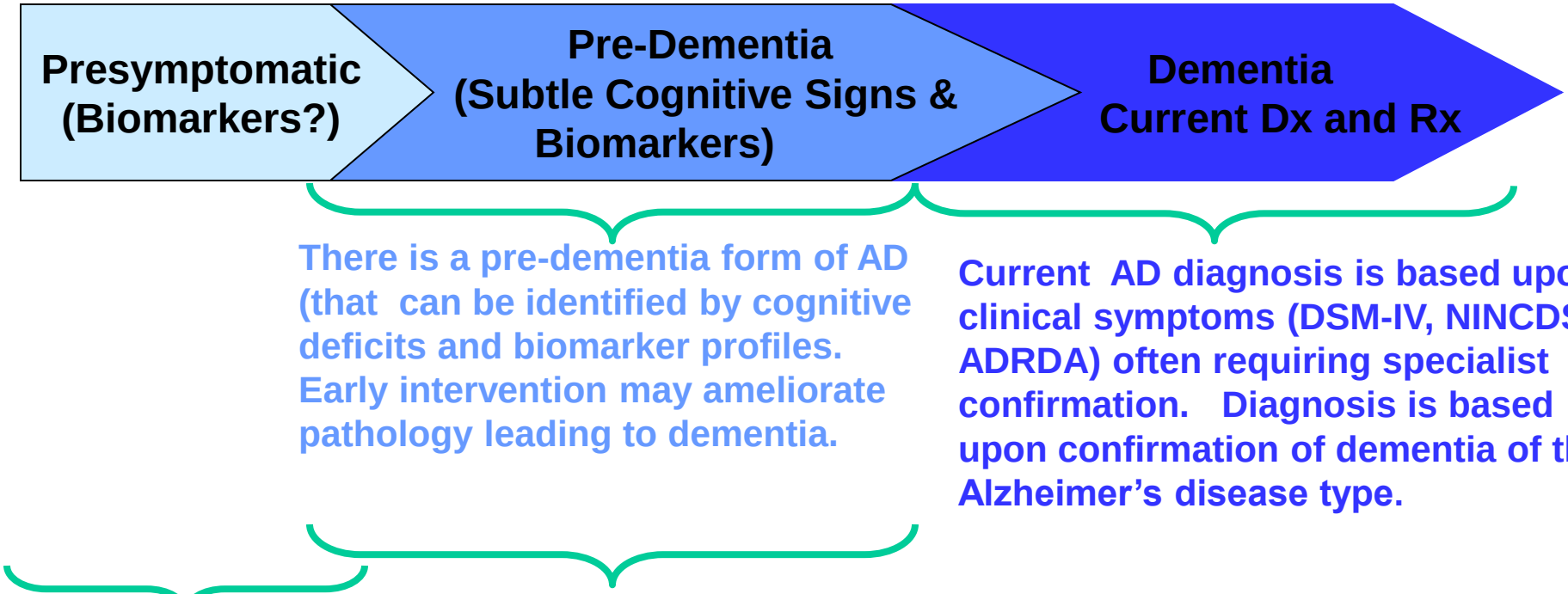
- Therapeutic goal/ Target selection
  - Stringent criteria –Clinical target validation emphasis- AMYLOID FOR AD
- Biomarker with Molecule Progression
  - Qualified biomarker associated with target mechanism
  - Sharing biomarker for molecule and therapeutic decision making
  - Clear strategy for use of biomarker: development support or commercial opportunity (companion diagnostic)
- In Vivo Model – Mechanism (Pathophysiology?)
  - Animal model that can at least model target mechanism – AMYLOID
  - Replicating data across labs
- Proof of Concept (PoC) trial possibilities
  - A well aligned, translatable, pathway to clinical PoC in patients

MODELS OF AD FOCUSED ON AMYLOID THEORY & USED TO SELECT AGENTS TO TEST HYPOTHESIS IN HUMANS



When and How to Test Amyloid Hypothesis?

The Progression of Alzheimer's Disease



Providing Tools to Test Hypotheses

- Measures of Drug Interactions with Target such as amyloid developed by academia and/or industry in various partnerships
- Measures of Disease State and Progression Mostly NIH Funded
- Measures of both classes applied to drug development ultimately require regulatory acceptance and pre competitive consortia model where tools are used across field

Therefore: Alzheimer's Disease Neuroimaging Initiative (ADNI) to Develop Tools for Field

ADNI 2 Structure – Extension of ADNI 1

Private/Philanthropic

+

Public

FNIH
Foundation for the National Institutes of Health

U.S. NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

FDA

NIBIB, NINDS, NIMH and other ICs

ADNI Executive Steering Committee

PI: Mike Weiner

Administrative Core: UCSF

PET Core: Berkeley: Jagust

MRI Core: Mayo: Jack

Clinical Core: UCSD: Aisen; Mayo: Petersen

Biomarkers Core: UPenn: Trojanowski/ Shaw

Publications Core: Harvard: Green

Biostatistics Core: UCD: Beckett

Informatics Core: UCLA: Toga

Pathology Core: WashU: Morris

Genetics Core: Indiana: Saykin

57 Clinical Sites: ADNI PIs and Cores

ADNI FUNDING
(cooperative agreement)

- ADNI1 (2004-2010)
- Total funding $60+ million/6 years
  - $40+ Million provided by NIH
  - $20+ Million provided by industry and other private partners through FNIH
- ADNI2 (2010-2015)
- Approximately the same amounts as ADNI1

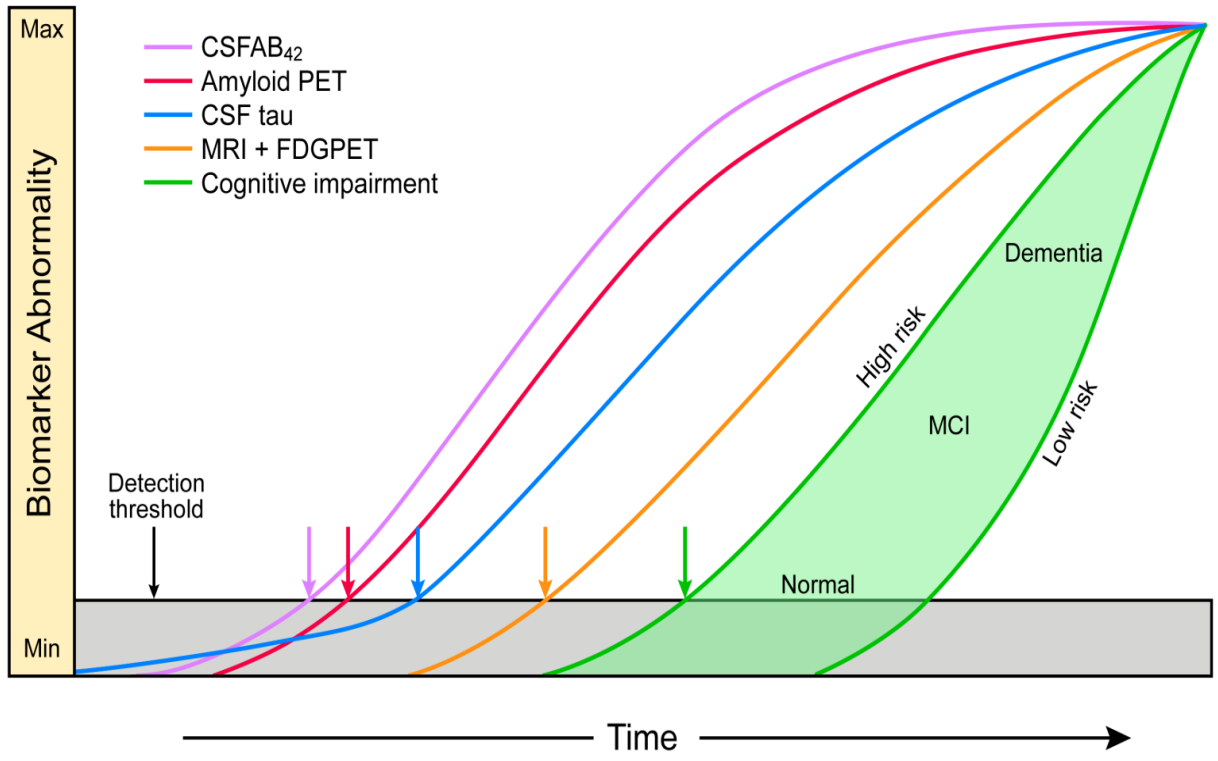
Summary: ADNI

- Standardization: imaging, biomarkers
- Neuroscience: relationships among biomarker trajectories elucidate neurobiology
- Earlier diagnosis: Support presymptomatic AD
- Trials: new understanding of biomarkers has facilitated interventional studies in very early AD
- Data sharing: ADNI has demonstrated the power of real-time public data sharing
- Collaboration: academia, industry, non-profits, regulatory agencies world-wide

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

Lancet Neurol 2013



Now Stage by Biomarkers & Target Mechanism

The Progression of Alzheimer's Disease

Potentially select at risk subjects before marker is +

Require objective biomarker to assure Dx, utilize other markers of drug effect to set dose and combine clinical and biochemical measures to characterize course

Utilize symptom measures but want evidence of drug effect at target and enhanced brain function prior to efficacy studies

True Prevention Opportunity?

Prevention of Dementia In Patients with Cognitive Complaint.

Treatment of Dementia:
Clearance of Toxic Amyloid?