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 (\( \gamma \)-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

- **Presymptomatic** (Biomarkers?)
- **Pre-Dementia** (Subtle Cognitive Signs & Biomarkers)
- **Dementia** Current Dx and Rx

There is a pre-dementia form of AD (that can be identified by cognitive deficits and biomarker profiles. Early intervention may ameliorate pathology leading to dementia.

Current AD diagnosis is based upon clinical symptoms (DSM-IV, NINCDS-ADRDA) often requiring specialist confirmation. Diagnosis is based upon confirmation of dementia of the Alzheimer’s disease type.

Best Prevention Opportunity?

**Prevention of Dementia In Patients with Cognitive Complaint.**

Treatment of Dementia: Clearance of Toxic Amyloid?
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

ADNI Executive Steering Committee
- PET Core: Berkeley: Jagust
- MRI Core: Mayo: Jack
- Clinical Core: UCSD: Aisen
  Mayo: Petersen

PI: Mike Weiner
Administrative Core: UCSF
Biomarkers Core: UPenn: Trojanowski/ Shaw
Informatics Core: UCLA: Toga
Genetics Core: Indiana: Saykin

Biostatistics Core: UCD: Beckett
Publications Core: Harvard: Green
Pathology Core: WashU: Morris

57 Clinical Sites: ADNI PIs and Cores

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

FDA
NIBIB, NINDS, NIMH and other ICs

Abbott
Amorfix
AstraZeneca
Bayer HealthCare
BIOCLINICA
biogen idec
Bristol-Myers Squibb
Eisai
Genentech
INGENIOGENICS
JANSSEN
Janssen Alzheimer Immunotherapy
Johnson & Johnson
Novartis
Pfizer
IXICO
Roche
SERVIER
Synarc
Takeda
Merck
Medpace
Canadian Institutes of Health Research
Instituts de recherche en santé du Canada
Meso Scale Diagnostics, LLC.
alzheimer's association®

ADNI 2 Structure – Extension of ADNI 1
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
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

Now Stage by Biomarkers & Target Mechanism

The Progression of Alzheimer’s Disease

- **Presymptomatic Biomarkers**
  - Potentially select at-risk subjects before marker is +

- **Pre-Dementia (Subtle Cognitive Signs & Biomarkers)**
  - Require objective biomarker to assure Dx, utilize other markers of drug effect to set dose and combine clinical and biochemical measures to characterize course

- **Dementia Current Dx and Rx**
  - Utilize symptom measures but want evidence of drug effect at target and enhanced brain function prior to efficacy studies

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True Prevention Opportunity?

- Prevention of Dementia in Patients with Cognitive Complaint.

- Treatment of Dementia: Clearance of Toxic Amyloid?