Identifying and Overcoming Challenges During Early Clinical Development of Alzheimer’s Disease Interventions

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Disclosures

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Outline of Talk

• Challenges in early clinical development in Alzheimer’s disease

• Alzheimer’s disease therapeutic targets

• Approaches to inform decision making
  – PET Imaging to establish target engagement
  – BACE inhibitors targeting Aβ as therapeutic target
  – Tau as therapeutic target: PET Imaging to enable early decision-making
Challenges in Alzheimer’s Disease Drug Development

- **Target selection**
  - Preclinical models of limited utility in predicting clinical efficacy
  - Difficult to model disease complexity
- **Clinical trials are often prohibitively long, large & expensive**
  - Clinical endpoints are noisy
  - Recruitment is challenging
  - Patients often have mixed pathology
- **Thus, critical need for biomarkers to:**
  - Inform dose selection
  - Stratify patients
  - Predict clinical outcomes
Alzheimer’s Disease Target Selection

Myriad of Potential Therapeutic Targets

M Citron

Nature Reviews | Drug Discovery
Strategy for Target Selection: Focus on Causal Human Biology

- Human Genetics
- Human Pharmacology
- Known Disease Pathology
- Disease Progression Biomarkers
- Genetically Defined Patient Cohorts
- Innovative tPharm Trials
- Disease Relevant Phenotypic Assays
- Established Pathophysiology In novel model
- Translatable Animal Models
- Translational PKPD Modeling

Causal Human Biology
Pharmacological Validation
Establishing Human Clinical Translation
Goals of Early Clinical Development

Use small, early stage clinical trials where safety, PK and PD can be densely interrogated

Confirm biological hypothesis with a focus on translatable pharmacology
  • Leverage PET capabilities to confirm target engagement
  • Minimize variability and use biomarkers to enhance effect size
  • Measure endpoints (safety or efficacy) with a faster readout than the registration endpoint

Identify dose for efficacy trials; leverage quantitative modeling approaches
PET Target Occupancy and Integrated Modeling to Inform Dose Selection

- Use adaptive design focused on establishing receptor/enzyme occupancy - plasma concentration relationship to establish minimal effective dose to test in PoC trials

**Receptor/Enzyme Occupancy**

**Repeated Dose Simulations**
Amyloid hypothesis and Alzheimer’s disease: the role of the APP gene and BACE1 in disease initiation

Causal human biology

- Aβ deposition in senile plaques
- APP, PSEN1, PSEN2 mutations cause FAD, increase Aβ cleavage
- APP-A673T variant reduces AD risk, decrease Aβ cleavage
MK-8931 is Potent, Competitive Inhibitor of BACE1 and BACE2

MK-8931: Aβ lowering in Cynomolgus Monkey CSF and Brain

- MK-8931 reduces CSF Aβ in rodents (not shown) and cisterna magna cannulated Cynomolgus monkeys
- Aβ kinetics from cortex to CSF result in greater Aβ lowering in cortex than CSF

![Graph showing Acute Cyno. Monkey CSF Aβ40](image)

![Graph showing Monkey CSF vs. Cortex Aβ40](image)

- MK-8931, po
MK-8931: Chronic CSF and Cortical Aβ Lowering in Monkey

- Tissues collected 4 hours following the last oral dose
- MK-8931 was well tolerated over 9 months of daily oral dosing.

9 month chronic dosing of MK-8931 in Cynomolgus monkeys

* p<0.001 Dunnet's anova

B Mattson & M Kennedy
Assessment of Pharmacodynamic Effects of BACE1 Inhibition in Human

- Indwelling CSF catheters utilized to monitor effects on sAPPβ and Aβ peptides following administration of MK-8931
  - sAPPβ assessed as a direct pharmacodynamic measure
  - Generation of Aβ40 and Aβ42 dependent on activity of γ-secretase
MK-8931 lowers Aβ levels >90% in CSF from healthy volunteers and Alzheimer’s disease patients

Multi-dose, healthy volunteers

Multi-dose, AD patients

CSF Aβ40 levels

Placebo (N=10)  MK-8931 150 mg (N=9)
MK-8931 10 mg (N=6)  MK-8931 250 mg (N=9)
MK-8931 40 mg (N=6)
Exposure-Response Model of BACE1 Inhibition of Amyloid Pathway

- Sigmoid Emax model best describes CSF modulation of Aβ and sAPPβ
  - Model represents major steps in production of β-amyloid including brain production, distribution to CSF and baseline drift
  - Transit compartment accounted for delay between brain and lumbar CSF Aβ & sAPPβ concentrations
- Simultaneously fit Aβ40, Aβ42 and sAPPβ individual time course data
- Single drug action (i.e., inhibition of BACE1) describes all data
- Suggests high degree of correlation in inhibition of brain production of Aβ40, Aβ42 and sAPPβ and CSF concentrations of these analytes

J Stone & H Kleijn
Simulations: MK-8931 Exposure-Response Model
Predicted Steady-State Response with Daily Dosing

- Consistent dose-response in steady-state median reduction of CSF Aβ40, Aβ42 & sAPPβ for healthy volunteers and Alzheimer’s disease patients
  - 90% confidence intervals (shaded area) based on uncertainty in parameter estimates
- Simulation of individual distributions indicates:
  - 12 mg QD: >98% of patients with at least 50% reduction of CSF Aβ40
  - 40 mg QD: >94% of patients with at least 80% reduction of CSF Aβ40

J Stone & H Kleijn
**Approaches to tau therapy:**

- **Tau immunotherapy:** block the spread of secreted tau dependent pathology and improve clearance.

- **Tau post-translational modification:** O-GlcNAcase inhibition reduces pathological tau in transgenic models

- **Tau aggregation/assembly inhibitors:** reduce and disrupt NFT formation

**Causal human biology**

- Tau aggregates in wide range of neurodegenerative diseases (e.g., AD, PSP, CBD, Pick’s disease)

- Tau mutations cause FTDP-17; lead to increase in Tau aggregation
Progression of Tau Pathology Correlates to Cognitive Decline

- Limited biomarkers to inform program decision making
- Direct visualization of pathology could guide clinical program for AD as well as other neurodegenerative diseases with tau pathology

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<tr>
<th>Alzheimer’s disease</th>
<th>CBD</th>
<th>DLB</th>
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<td>Chronic traumatic encephalopathy</td>
<td>Corticobasal degeneration</td>
<td>Dementia with Lewy bodies</td>
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<td>Pick’s disease</td>
<td>CTE</td>
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Abner, E et al. J Alz Dis. 2011
Tau-Specific PET tracers

Tau imaging may provide a critical decision making tool to enable drug discovery for neurodegenerative diseases

Tau PET tracer provides potential for:

**Proof of mechanism**
Early PD biomarker for Tau; targeting therapy response

**Disease progression**
Evaluate disease modification in resource sparing clinical trials

**Patient selection**
Enrollment in prodromal and presymptomatic clinical trials

![Amyloid and Tau PET imaging](image)
AV-1451 (T807) Avid/Lilly: Tau PET Tracer

- $[^{18}F]$AV-1451 has a small specific signal in prodromal/mild AD subjects (MMSE ≥ 20)
- Mean annualized change in AV-1451 cortical SUVR = ~3.5% (in 63 amyloid-positive subjects)
- Recognized off-target binding and unstable kinetics may limit utility for longitudinal studies

**Cross-sectional data in AD patients (MMSE vs. Tau signal)**

**Longitudinal data in AD patient**
(60 years MMSE = 26 → 24 over ~13 months)

*Discovery of more sensitive Tau PET tracer may further enable clinical decision making for drug discovery*
Challenges in Alzheimer’s Disease Drug Development

- Preclinical models of limited utility in predicting clinical efficacy
  - Focus on targets linked to pathophysiology of disease
- Critical need for biomarkers to:
  - Inform dose selection
    - Establish target engagement and biological activity in the CNS
    - Leverage modeling & simulation
  - Stratify patients
    - Potential for PET imaging and/or fluid biomarkers that identify patients with AD pathology
- Clinical trials are often prohibitively long, large, and expensive; recruitment is challenging
  - Development of tools that can be linked to clinical outcomes
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