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

Mark Forman, MD, PhD

March 11, 2016

# Disclosures

- Employee of Merck and own stock/stock options in Merck
- Some of the work presented today (e.g., BACE inhibitor MK-8931) was funded by Merck and Co., Inc.

# Outline of Talk

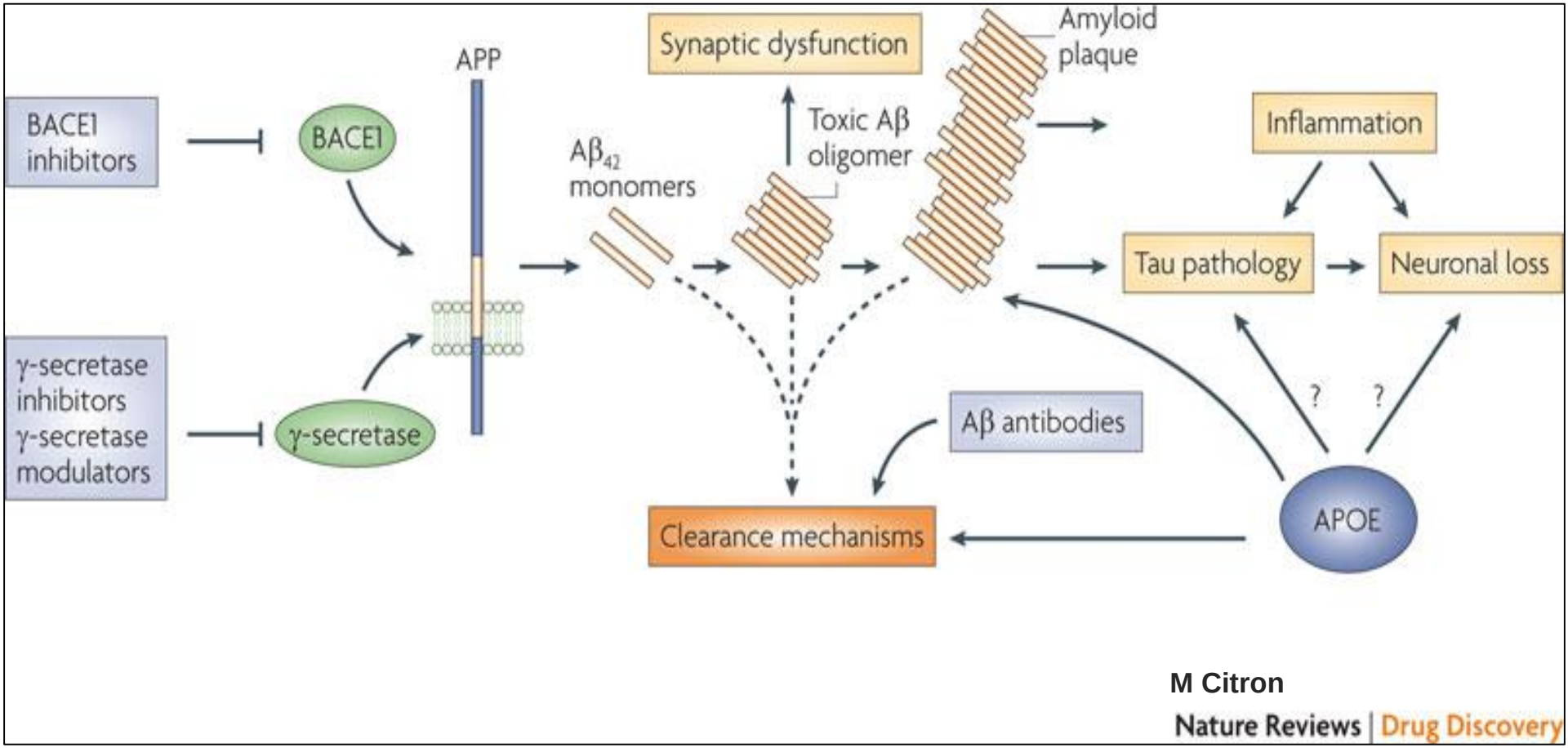
- Challenges in early clinical development in Alzheimer's disease
- Alzheimer's disease therapeutic targets
- Approaches to inform decision making
  - PET Imaging to establish target engagement
  - BACE inhibitors targeting Aβ as therapeutic target
  - Tau as therapeutic target:  PET Imaging to enable early decision-making

# Challenges in Alzheimer's Disease Drug Development

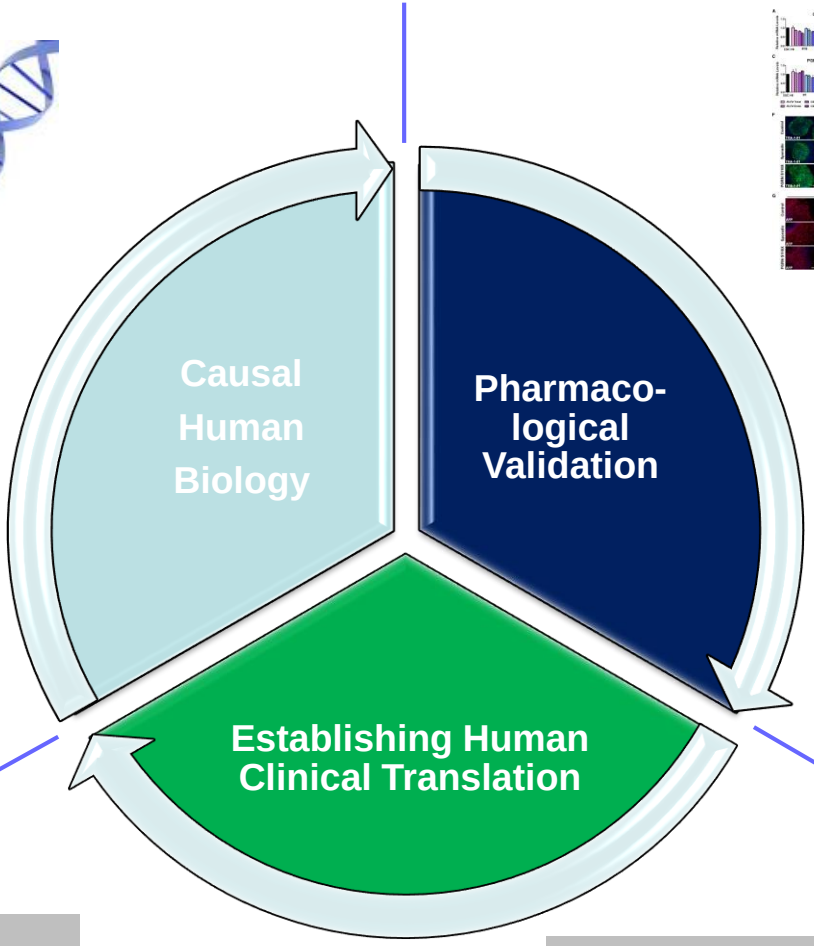
- Target selection
  - Preclinical models of limited utility in predicting clinical efficacy
  - Difficult to model disease complexity
- Clinical trials are often prohibitively long, large & expensive
  - Clinical endpoints are noisy
  - Recruitment is challenging
  - Patients often have mixed pathology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

# Alzheimer's Disease Target Selection

## Myriad of Potential Therapeutic Targets



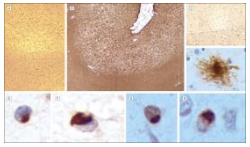
# Strategy for Target Selection: Focus on Causal Human Biology



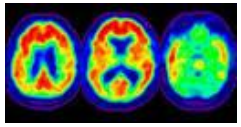

*Human Genetics*

*Human Pharmacology*

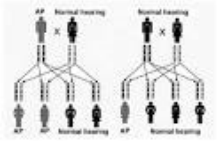
*Known Disease Pathology*



*Disease Progression Biomarkers*

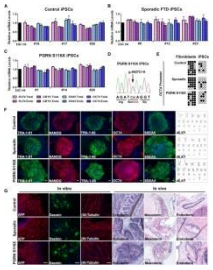


*Genetically Defined Patient Cohorts*

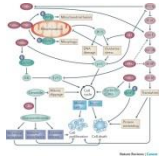


*Innovative tPharm Trials*

*Translational PKPD Modeling*



*Disease Relevant Phenotypic Assays*



*Established Pathophysiology In novel model*

*Translatable Animal Models*

# 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**

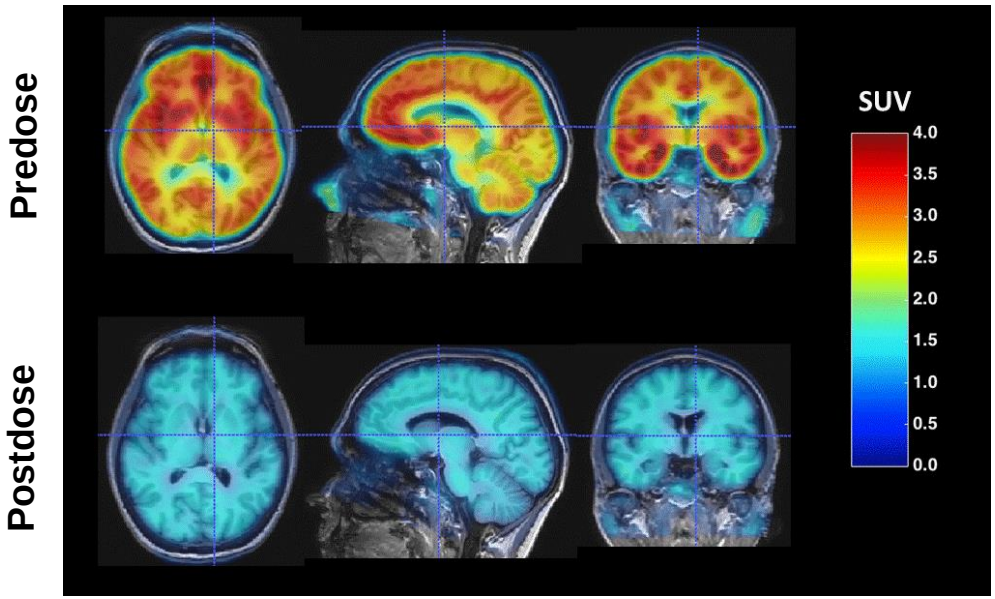
- Leverage PET capabilities to confirm target engagement
- Minimize variability and use biomarkers to enhance effect size
- Measure endpoints (safety or efficacy) with a faster readout than the registration endpoint

**Identify dose for efficacy trials; leverage quantitative modeling approaches**

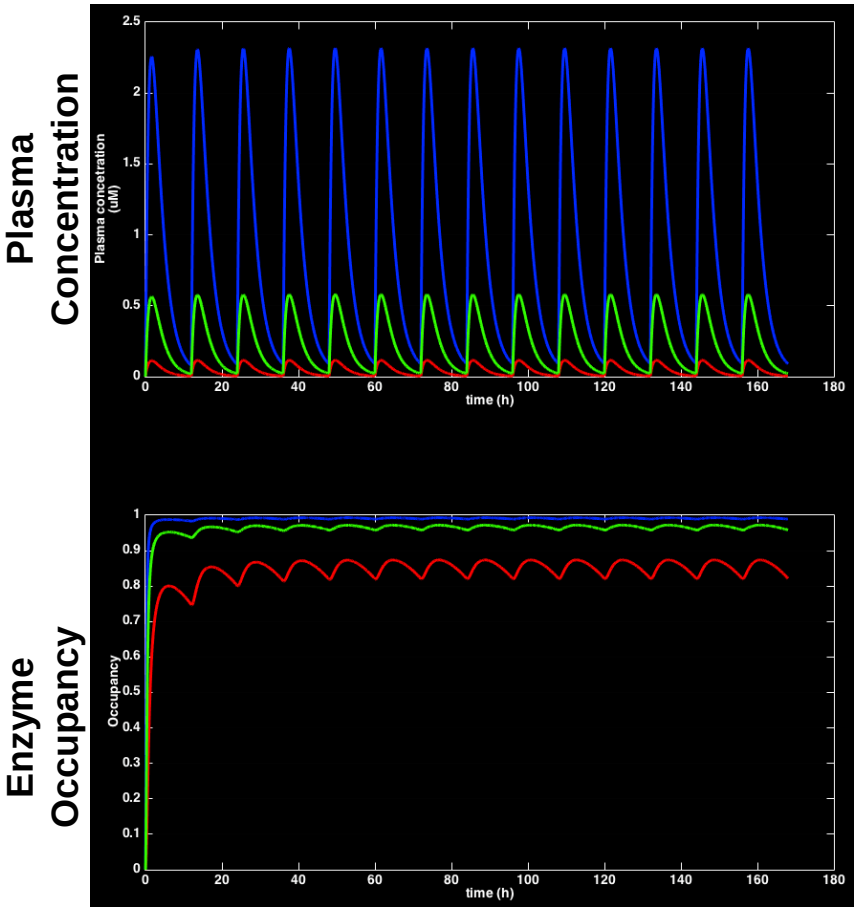
# PET Target Occupancy and Integrated Modeling to Inform Dose Selection

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

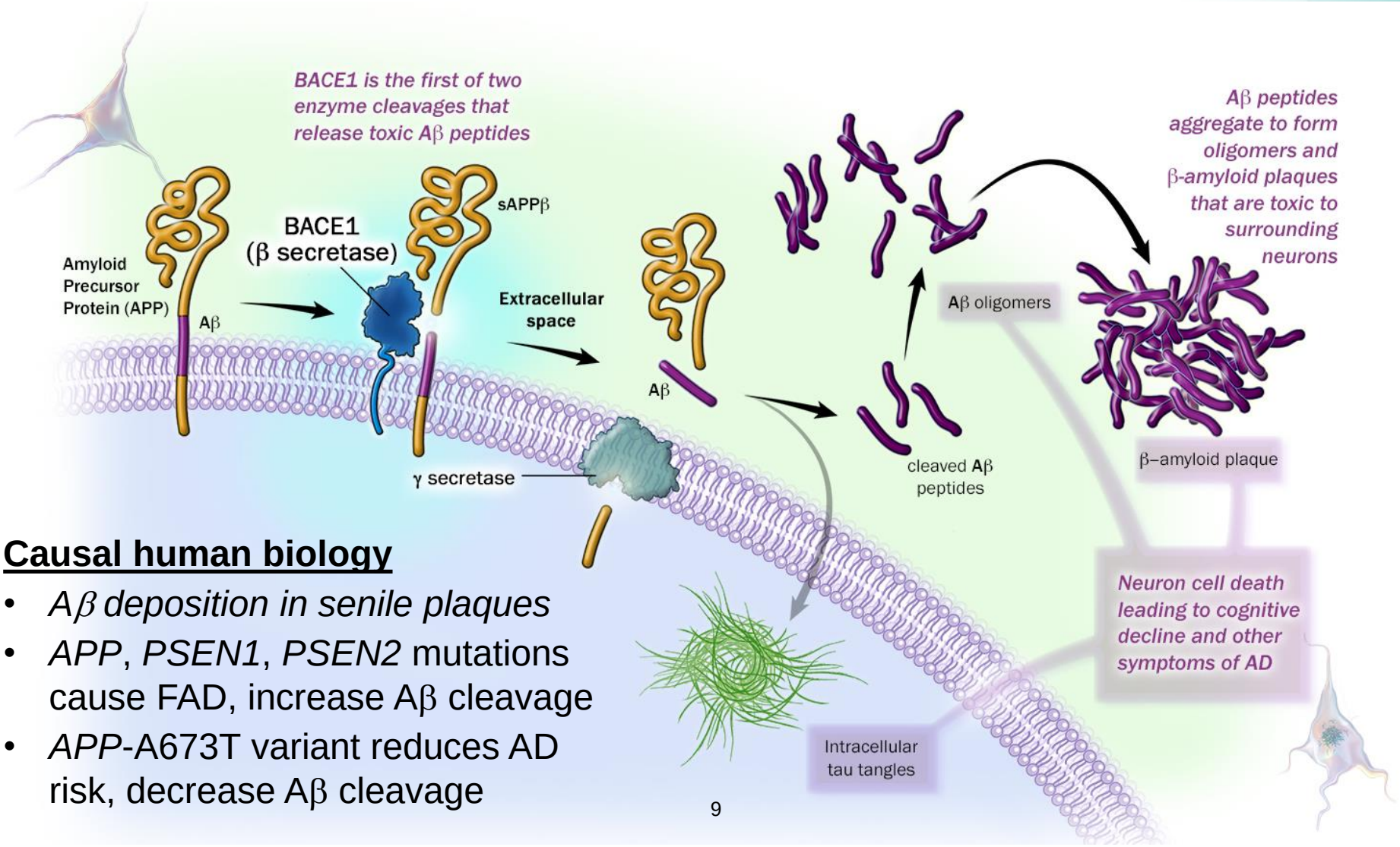
**Receptor/Enzyme Occupancy**




**Repeated Dose Simulations**



# Amyloid hypothesis and Alzheimer's disease: *the role of the APP gene and BACE1 in disease initiation*

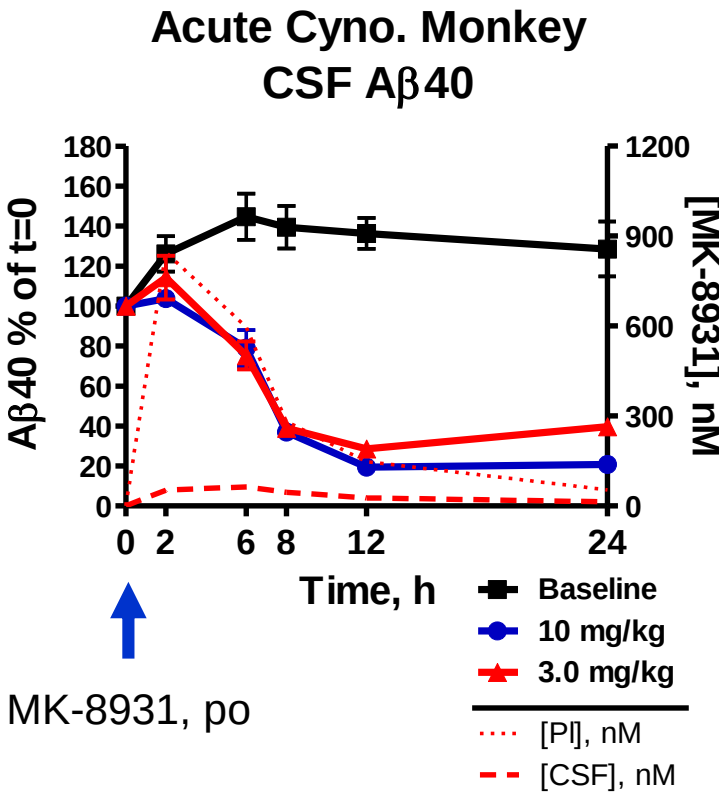


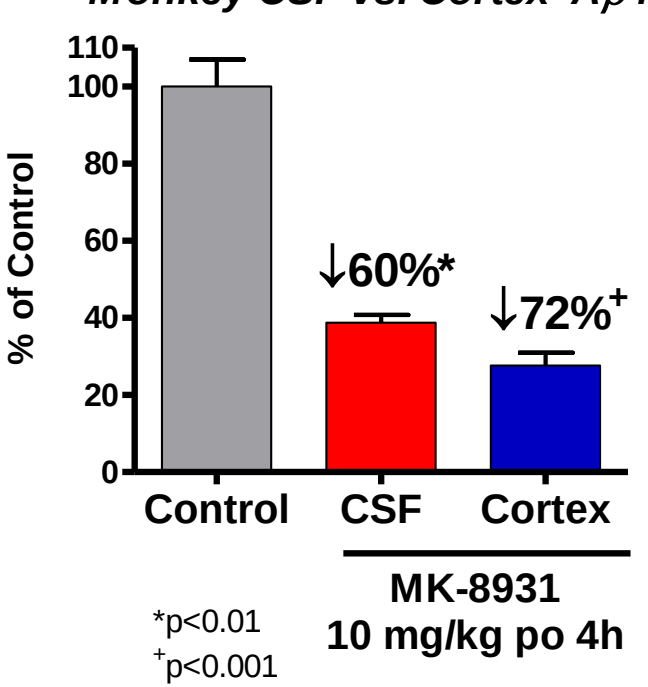

**Causal human biology**

- *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



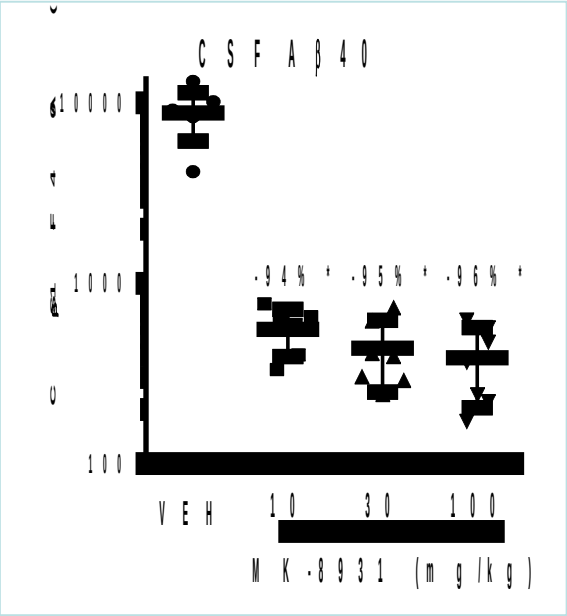

- MK-8931 reduces CSF Aβ in rodents (not shown) and cisterna magna cannulated Cynomolgus monkeys
- Aβ kinetics from cortex to CSF result in greater Aβ lowering in cortex than CSF

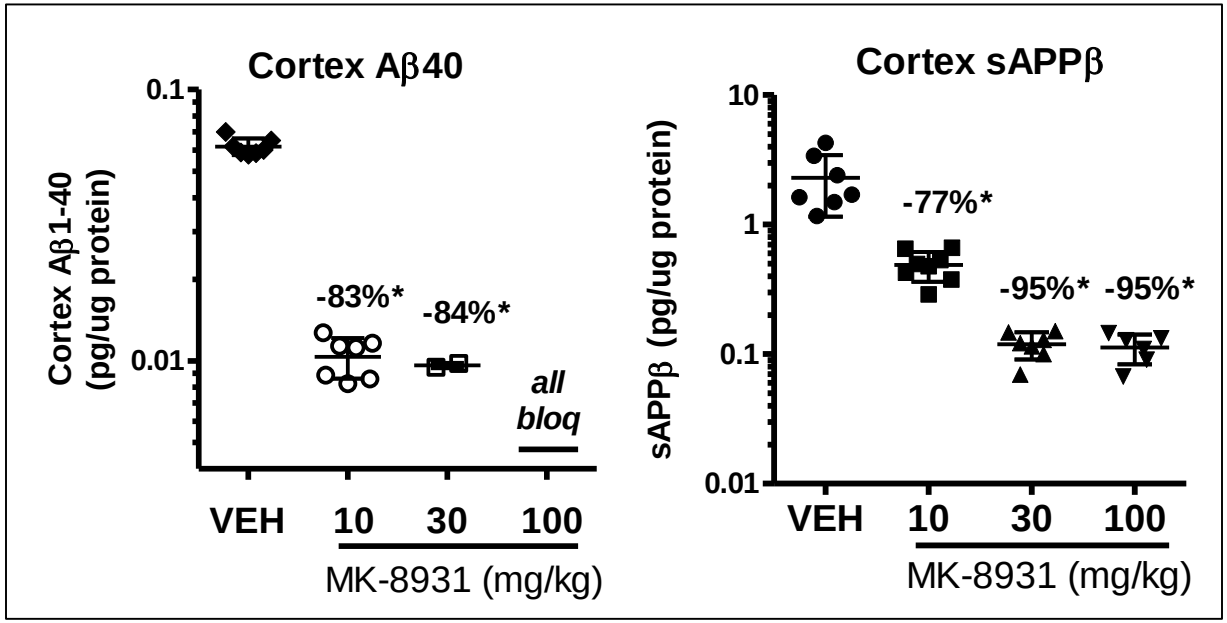


*M Kennedy*

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

➢ ***9 month chronic dosing of MK-8931 in Cynomolgus monkeys***




*p<0.001 Dunnet's anova

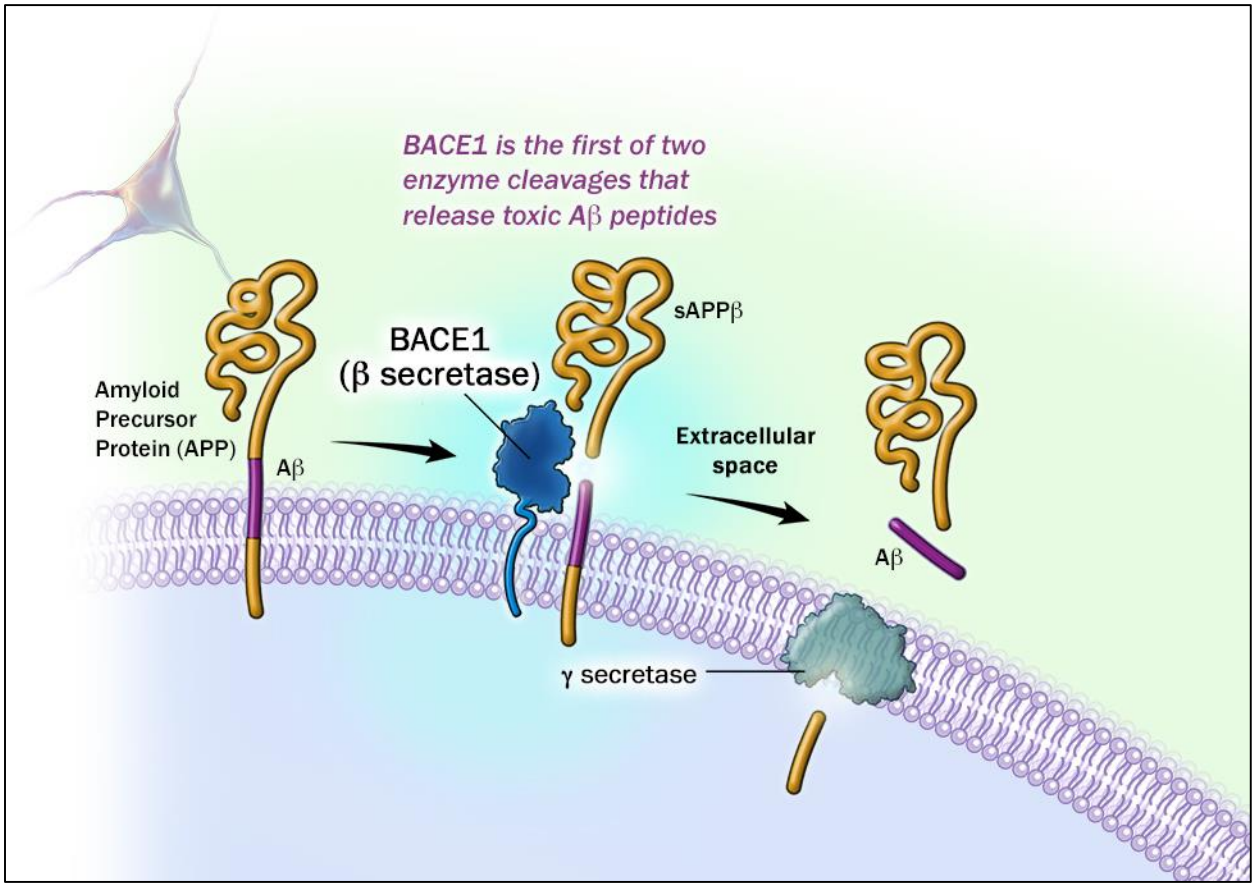
- Tissues collected 4 hours following the last oral dose
- MK-8931 was well tolerated over 9 months of daily oral dosing.



*B Mattson & M Kennedy*

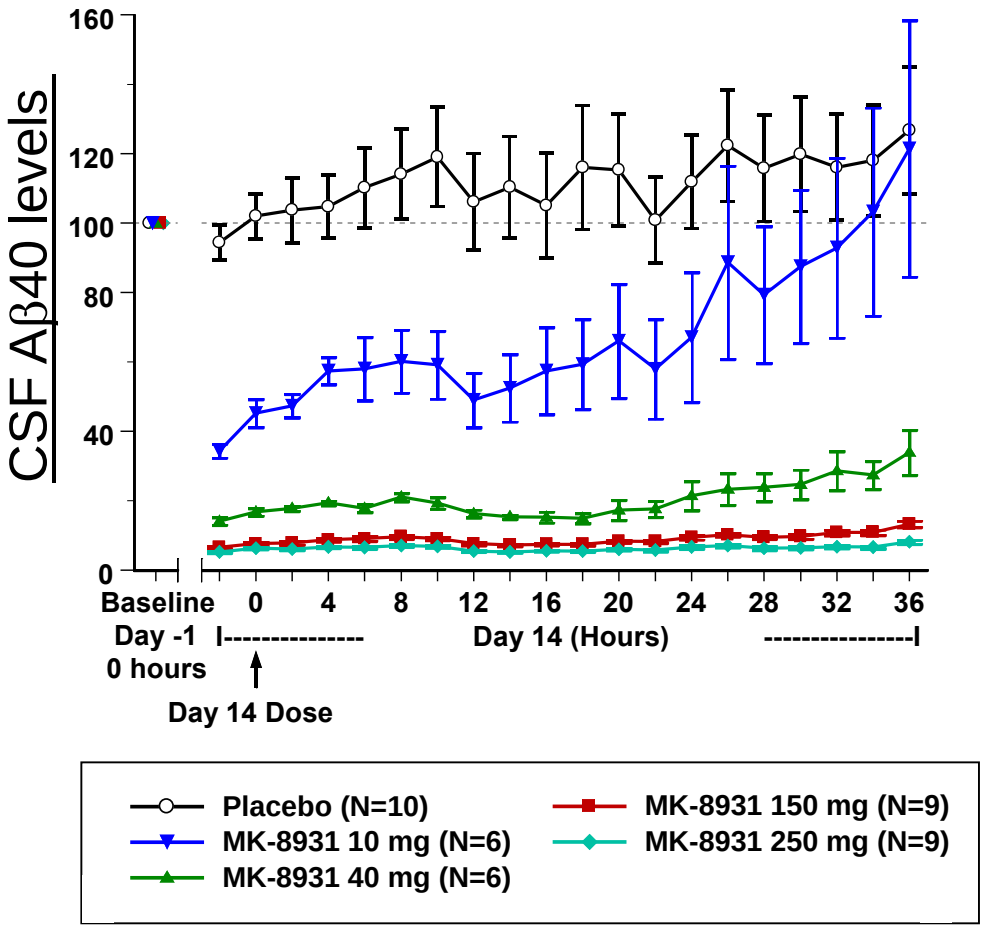
# Assessment of Pharmacodynamic Effects of BACE1 Inhibition in Human

- 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

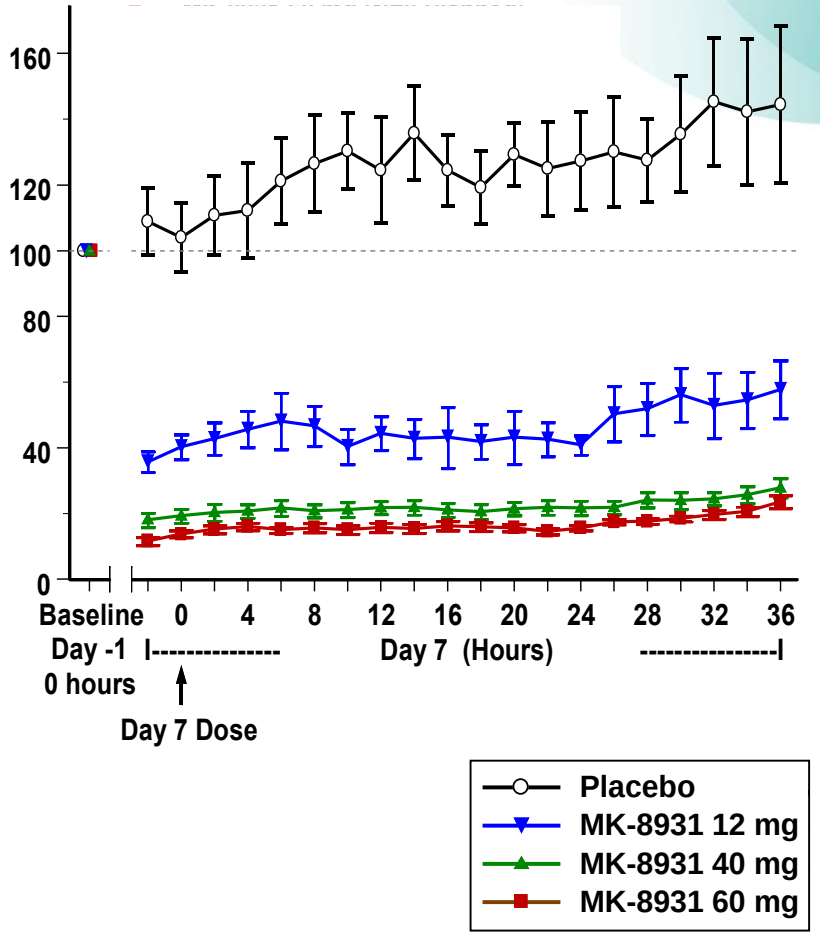


# MK-8931 lowers Aβ levels >90% in CSF from healthy volunteers and Alzheimer's disease patients

## Multi-dose, healthy volunteers




## Multi-dose, AD patients



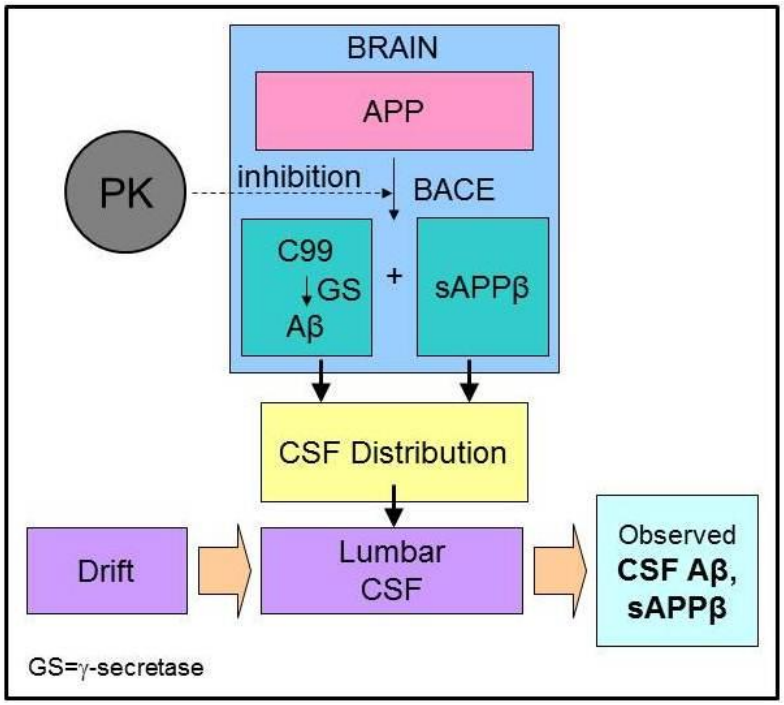


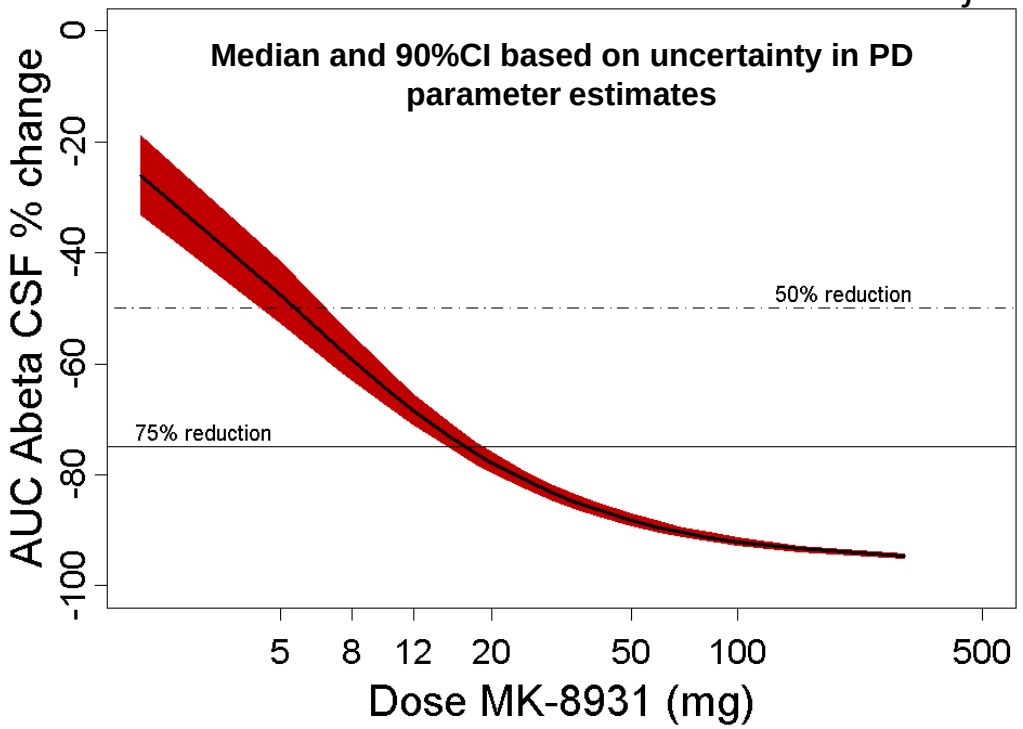

MERCK
Be well

# 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

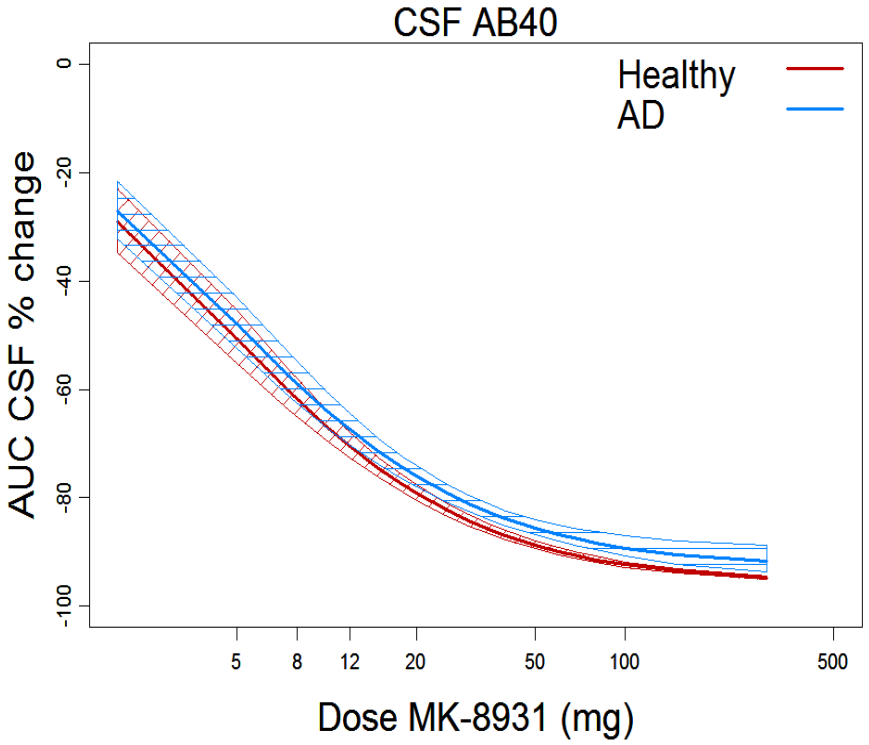
*J Stone & H Kleijn*

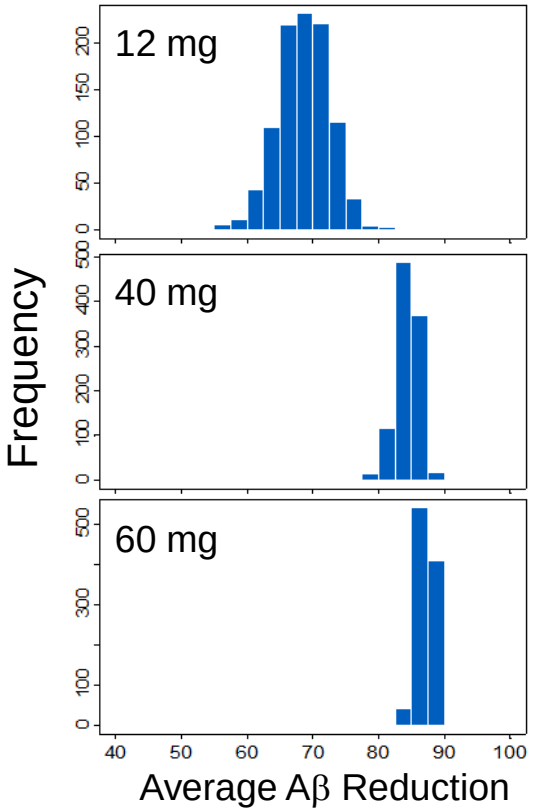


# Simulations: MK-8931 Exposure-Response Model Predicted Steady-State Response with Daily Dosing

- 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

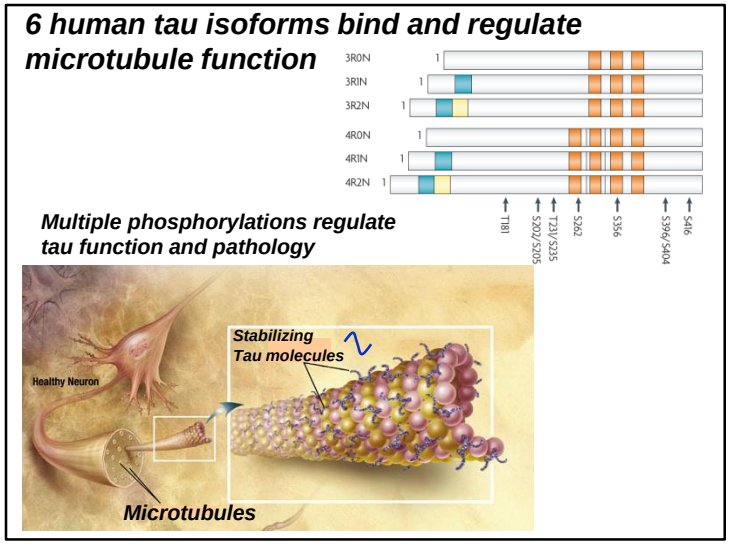


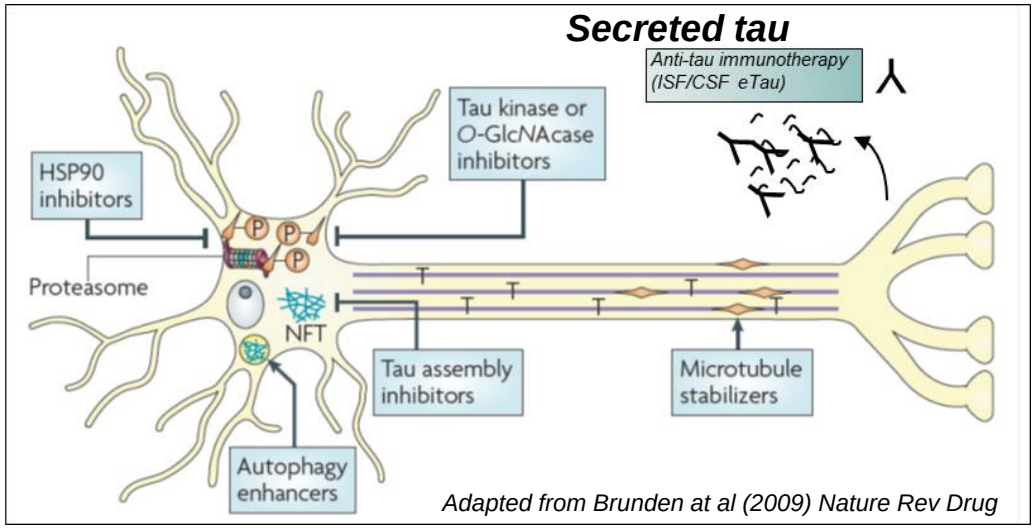






*J Stone & H Kleijn*

# Tau as a Therapeutic Target in Neurodegenerative Disease




## 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

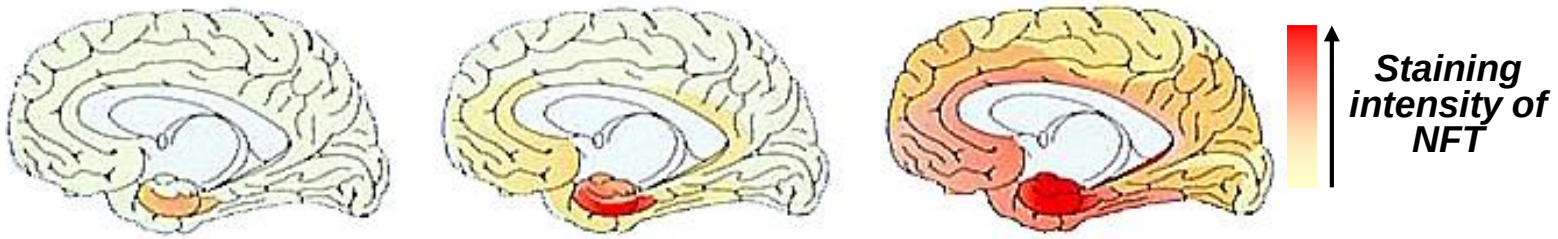
## Causal human biology

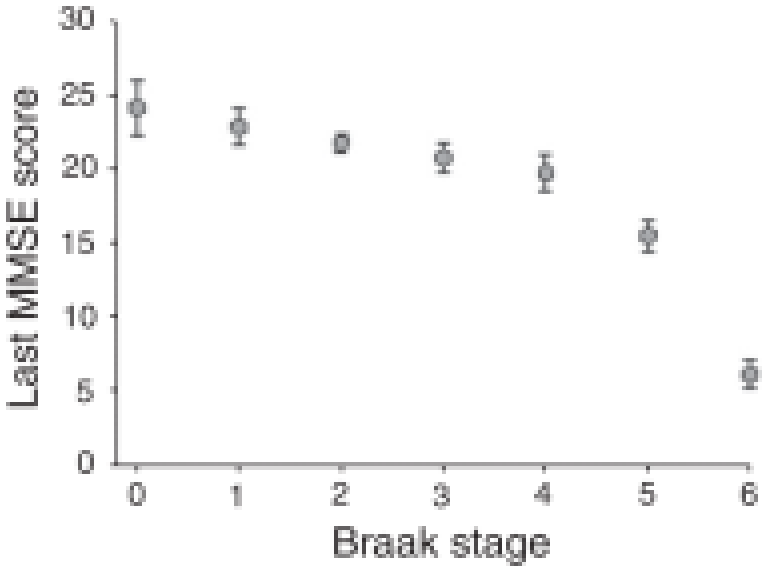
- Tau aggregates in wide range of neurodegenerative diseases (e.g., AD, PSP, CBD, Pick's disease)
- *Tau* mutations cause FTDP-17; lead to increase in Tau aggregation

# Progression of Tau Pathology Correlates to Cognitive Decline

**Clinically silent** → **Incipient AD** → **Fully developed AD**

transentorhinal stages I-II | limbic stages III-IV | neocortical stages V-VI




Abner, E et al. J Alz Dis. 2011

- 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

| | | |
|---|---|---|
| **Alzheimer's disease** | **CBD** Corticobasal degeneration | **DLB** Dementia with Lewy bodies |
| **CTE** Chronic traumatic encephalopathy | **PSP** Progressive Supranuclear Palsy | **Pick's disease** FTD with Tau pathology |

# Tau-Specific PET tracers

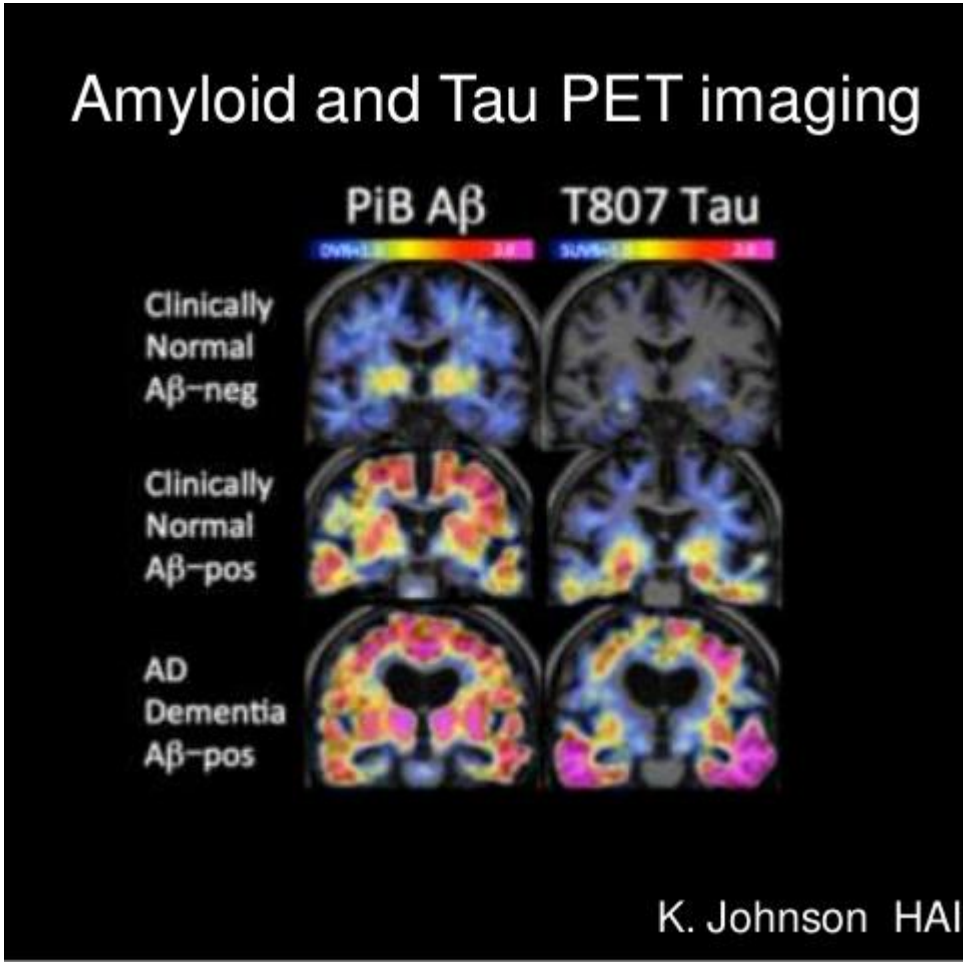
**Tau imaging may provide a critical decision making tool to enable drug discovery for neurodegenerative diseases**

**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**

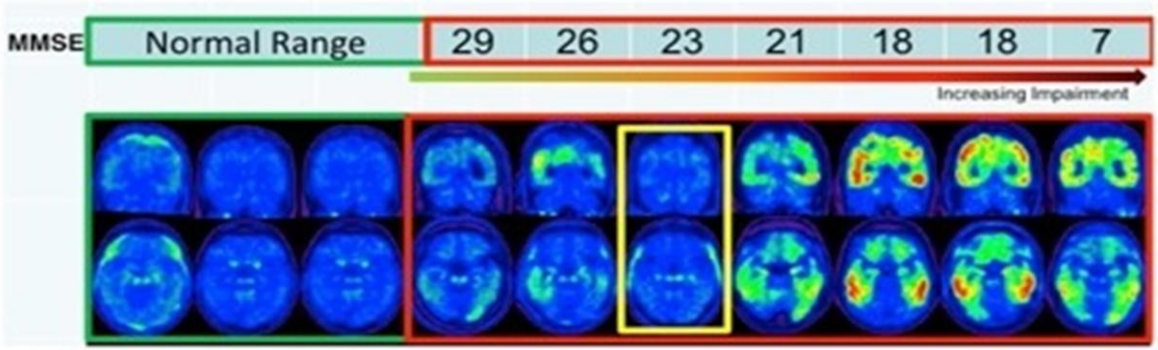
**Patient selection**
**Enrollment in prodromal and presymptomatic clinical trials**



# AV-1451 (T807) Avid/Lilly: Tau PET Tracer

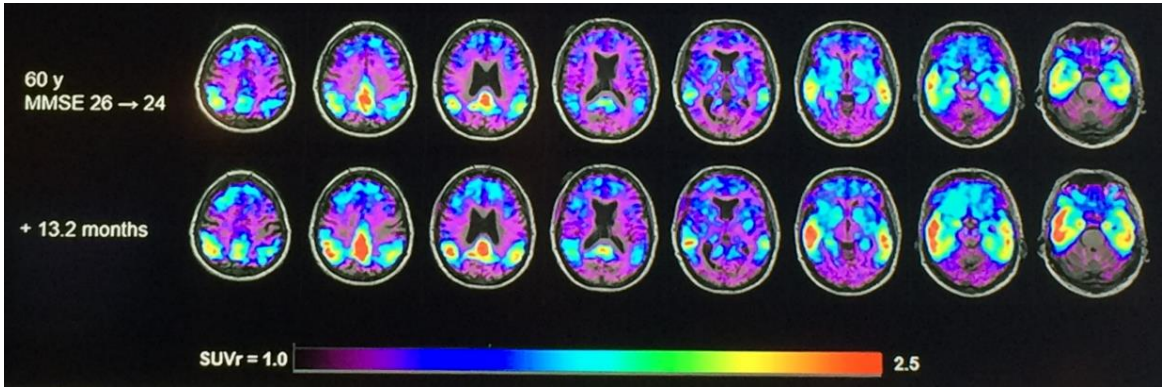
- [$^{18}$F]AV-1451 has a small specific signal in prodromal/mild AD subjects (MMSE ≥ 20)
- Mean annualized change in AV-1451 cortical SUVR = ~3.5% (in 63 amyloid-positive subjects)
- Recognized off-target binding and unstable kinetics may limit utility for longitudinal studies

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




AAIC, July 2013

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




HAI, Jan 2015

**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**

# Acknowledgments


**BACE**

- Jared Cumming
- Mike Egan
- Marissa Dockendorf
- Lynn Hyde
- Matt Kennedy
- Huub Kleijn
- Omar Laterza
- Britta Mattson
- John Palcza
- Eric Parker
- Jake Scott
- Andy Stamford
- Julie Stone
- Michael Tanen
- Matt Troyer
- Jack Tseng

**PET Imaging**

- Ruben Declercq
- Eric Hostetler
- Dan Jonathan
- Jung Hoon Lee
- Wenping Li
- Talahad Lohith
- Tom Reynders
- John Palcza
- Christian Salinas
- Punam Sandhu
- Sean Smith
- Arie Struyk
- Cyrille Sur
- Koen Van Laere
- Chandni Valiathan




MERCK
Be well

# Thank-you