THE NATURAL HISTORY OF Aβ-AMYLOID DEPOSITION

- Meaningful benchmarks for considering treatment effects of preclinical AD in sporadic Alzheimer’s disease -

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Remote computerized detection of pre-clinical cognitive disorders - Bridging the gap between cognitive training and cognitive assessment

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INTERRELATIONSHIPS BETWEEN AMYLOID & TAU
SYNAPTIC LOSS
Hypothesis: Aβ42 produced at synapses within mitochondria-associated membranes is toxic to mitochondria

AD
CONTROL
courtesy Robert Terry, 2005

NEURONAL LOSS

Alzheimer, A. Zeitschrift für die gesamte Neurologie und Psychiatrie 4, 356-385 (1911)
Aβ TOXICITY

NATURAL HISTORY OF THE AMYLOID PLAQUE
How old are end stage amyloid plaques isolated from post mortem brains?

approximately 30 years
(determined as rate of amino acid racemization)

NATURAL HISTORY OF AD & THE WINDOWS FOR PRIMARY PREVENTION SECONDARY PREVENTION TREATMENT PALLIATIVE CARE
### Natural History of Alzheimer’s Disease

#### PRIOR TO ONSET OF PATHOGENESIS

**Prodrome/Silent Clinical Phase:** ≈ 20-30 Years

- **Disease:** Dementia as main symptom (loss of acquired intellectual capabilities)

#### SECONDARY PREVENTION

**MCI:** <5 years (neuronal loss: 36.5%)*
(75% conversion to Alzheimer’s disease in five years)

#### TREATMENT

**Clinical phase:** 2-20 years of duration

- **Mild:** 3 years (neuronal loss: 60%)*

#### PALLIATIVE CARE

- **Moderate:** 3 years (neuronal loss: 60-90%)*
- **Severe:** 3 years (neuronal loss: 90%)*

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Aβ PRODUCTION & CLEARANCE IN THE HUMAN BRAIN IN HEALTH & DISEASE

β-SECRETASE (BACE 1)

APP → Aβ → γ-SECRETASE

Aβ
The SILK (Stable isotope labeling kinetics) METHOD

Labeling Aβ with 13C-leucine allows determination of brain Aβ synthesis in CSF.

RESULT: ≈8 percent (≈580 ng) of brain Aβ made and cleared each hour.

Unaltered Aβ synthesis in AD

Aβ kinetics in the CSF of 12 AD participants (red triangles) and 12 controls (blue circles)

Reduced $A\beta$ clearance rate in sporadic AD

hourly clearance rate from CSF drops by about 25%, or 145 ng/hour

Brain amyloid load in AD?
Aβ AMYLOID LOAD IN AD BRAIN?

According to our own estimates and published literature*, a total of 4 – 6 mg Aβ accumulates in Alzheimer’s disease.

Assuming that it takes three decades for Aβ to accumulate in the AD brain, Aβ likely aggregates at a rate of about 15-23 ng/hour.

This assumes that the rate of accumulation is a constant, which may not be the case.

*Cohen et al. 2013; PNAS 110, 9758-9763 (pnas.12184021109)
Amyloid PiB-PET confirms ≈30 years, 4.8 mg amyloid in AD brains, and a rate of about 28 ng/hour (20 years).

The "neuroeconomy" of Aβ

- Amyloid plaque:
  \( \approx 2 \times 10^{11} \) Aβ molecules
  \( \approx 1.4 \times 10^{-9} \) gram/plaque

- Amyloid load: 4.8 mg/brain
  \( \approx 3,4 \) million plaques/AD brain

- Amyloid growth rate: \( \approx 28 \) ng/hour (over 20-30 years)
  \( \approx 2\%-5\% \) of daily production
DOES AGE INFLUENCE CSF Aβ CLEARANCE?

PREVALENCE OF ALZHEIMER’S DISEASE DOUBLING EVERY 6.9-7.5 YEARS
AMYLOIDOSIS AND AGE > 73 YEARS profoundly impair the ability of Aβ42 to move freely through the central nervous system.
Age slows Aβ half-life 2.5fold - from 3.8 to 9.4 hours over five decades -

CSF-fractional Aβ turnover rates (FTR) are highly negatively correlated with age

(amyloid⁺: ▲; amyloid⁻: + & ○)

Diurnal fluctuations in CSF of Aβ42 essentially disappeared in people older than 73 who had no brain amyloid. Aβ42 amplitude declines 0.91pM per year in amyloid-negative individuals, but remains stable in the amyloid-positive group.

Associations Between β-Amyloid Kinetics and the β-Amyloid Diurnal Pattern in the Central Nervous System

Diurnal fluctuations of CSF Aβ42 essentially disappeared in people older than 73 who had no brain amyloid. This could be due to the 2.5-fold increase in half-life of Aβ42 in this age group as compared to young adults. The long half-life could set the stage for amyloid to begin to accumulate in some people.

WHY IS CSF Aβ42/Aβ40 RATIO A MEANINGFUL BENCHMARK OF AD?
CSF-Amyloid-β (Aβ)42 kinetics are altered at Aβ42/Aβ40 ratios <0.1 (brain amyloidosis) and at Aβ42/Aβ40 ratios ≈0.16-0.1.

Aβ deposition causes > 50% irreversible loss of soluble Aβ42 clearance

DIURNAL Aβ PRODUCTION & CLEARANCE IN THE HUMAN BRAIN IN HEALTH & DISEASE

β-SECRETASE (BACE 1)

APP

Aβ

γ-SECRETASE

Aβ
Associations Between β-Amyloid Kinetics and the β-Amyloid Diurnal Pattern in the Central Nervous System

In a young, healthy brain, soluble Aβ follows a predictable pattern, rising during the day when the brain is active, and falling each night, perhaps due to enhanced clearance during sleep.
Interstitial Aβ Amyloid is cleared most efficiently during non-REM sleep.


Natural nonREM sleep increases interstitial fluid (ISF) and liquid exchange between brain and CSF by 60%: increased drainage of Aβ

Slow-wave sleep (SWS) disturbances
50% increased plasma Aβ levels in aMCI subjects

Sanchdez-Espinoza MP, Atienza M, Cantero JL. Sleep deficits in mild cognitive impairment are related to increased levels of plasma amyloid-β and cortical thinning. Neuroimage 98,395-404 (2014)
Meaningful benchmarks for considering treatment effects of preclinical AD in sporadic Alzheimer’s disease

- **CSF [Aβ42/Aβ40] >0.16**
  - PET-amyloid-negative

- **CSF [Aβ42/Aβ40] ≈0.16-0.1**
  - PET-amyloid-negative

- **CSF [Aβ42/Aβ40] <0.1**
  - PET-amyloid-positive
Aβ BLOOD TEST

Two blood tests in preparation:

- Detection of Aβ42 aggregate conformation in blood by immuno infrared-sensor
- Detection of Aβ42/Aβ40 ratio in blood by mass spectrometry
AMYLOIDOCENTRIC TREATMENT TARGETS FOR PRIMARY AND SECONDARY PREVENTION OF SPORADIC ALZHEIMER’S DISEASE

Treatment target: PATHOLOGY
attenuate Aβ production and aggregation
increase Aβ clearance
attenuate tau aggregation

Treatment target: SYNAPTIC LOSS
increase cognitive reserve (threshold)
SUMMARY

Need SPECIFIC INTERVENTIONS/THERAPIES that lower Aβ production, or promote Aβ clearance.

Combinations of interventions targeting Aβ production and Aβ clearance should be explored (e.g. stress ↓, cognitive & physical exercise ↑, sleep ↑, nutrition, cvd ↓).

Clearing the AD brain of 4-6 mg of aggregated Aβ should not be an insurmountable objective.