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Do Clinical Results to Date Suggest that Drug Development Based on the Amyloid Hypothesis of Alzheimer's Disease is Dead?

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Program Objectives

1. Critically evaluate the validity and robustness of the pre-clinical and genetic models for amyloid in AD (briefly reviewed), especially focusing on pre-clinical and clinical translational assumptions;
2. Describe the experimental medicine models supporting, with high specificity and sensitivity, an amyloid hypothesis for disease progression in AD, i.e., briefly review ADNI and its international counterparts findings. Do these successes predict amyloid targeting drug's success?
3. Identify challenges in drug (small molecules and antibodies 'targeting amyloid') methodology, signal detection, and study design aimed at disease course modification and symptomatic claims in AD from recently conducted clinical trials;
4. Heavily focus on lessons learned and in suggesting improved approaches to evaluate efficacy and/or disease progression across the AD continuum for amyloid modifying therapies.

Given the recent 'discouraging' results, what is the path forward?

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In the News: "Gamma secretase inhibitor: Top doses terminated in prodromal trial due to safety concerns"

2011-02-17 BioPharm Insight by Anusha Kambhampaty

- BMS-708163 mild-to-moderate AD study assessed doses of 25, 50, 100 and 125mg/day, according to clintrials.gov. (to be presented at ICAD 2012)
- BMS dropped the two highest doses in the currently ongoing Phase II study of prodromal Alzheimer's (based on safety review of both studies, per BMS statement)
  - AE's in the higher dose range: skin rashes and GI upset
- "There was mention of potential for decline in cognition, which we interpreted as a response to the Lilly semagacestat study, but no specific language indicating more decline in treated patients compared to placebo", Dr. Brockington, PI, U of AL
- Do Animals Lie, when it comes to NOTCH specificity?

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Drugs in Development Based on the Amyloid Hypothesis

- Drug mechanism assumptions
- Ravi will introduce AD related gene/pre-clinical models
- Assuming amyloid is a valid biomarker for disease progression, and given the dose related changes in 'Aβ' for current drugs
  - What are the implications for the lack of efficacy of many Aβ modifiers in AD?
  - Do we have 'target' engagement?

- Inhibiting production of beta-amyloid
  - β or γ -secretase inhibitors
- Amyloid modulators

- Increasing clearance
  - "Active vaccines"
  - "Passive vaccines"
- Inhibitors of beta-amyloid aggregation

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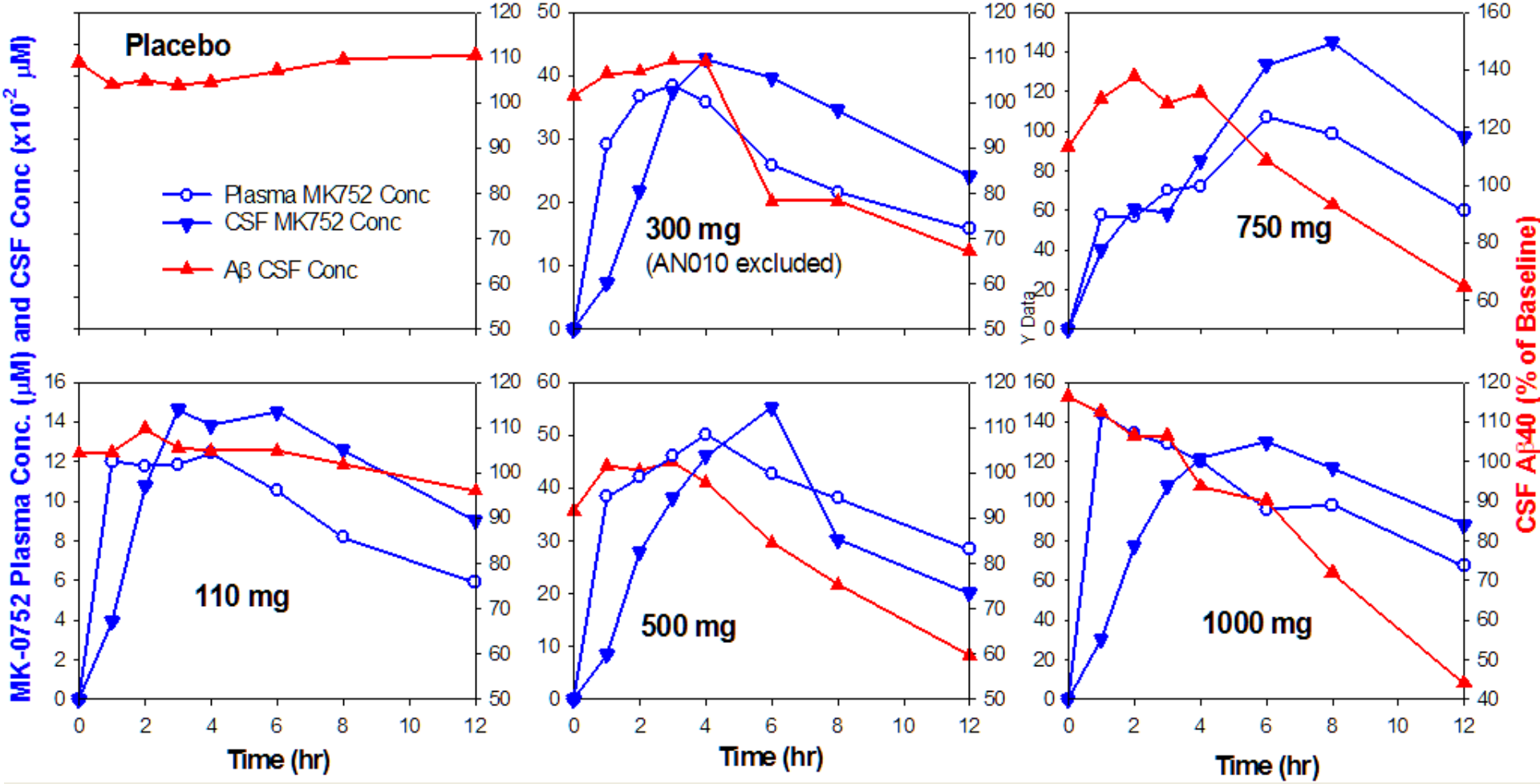
Mean MK-0752 Plasma and CSF Profiles and Aβ CSF Profiles After Single Doses

GSI's Demonstrate Dose Related Reductions in ABeta40/42 (n= 4-5 HNVs/group)



Rosen, et al. ICAD, Madrid, July 2006.

LY2811376 dose-dependent (PBO, 30 mg and 60 mg) BACE1 Inhibitor: Δ CSF Aβ

See, Ferenc Martenyi, et al. ICAD 2010

LY2811376 dose-dependent changes in CSF sAPPα and sAPPβ

See, Ferenc Martenyi, et al. ICAD 2010

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Changes in Aβ 42 with PPI-1019 an Amyloid 'Aggregation Inhibitor'

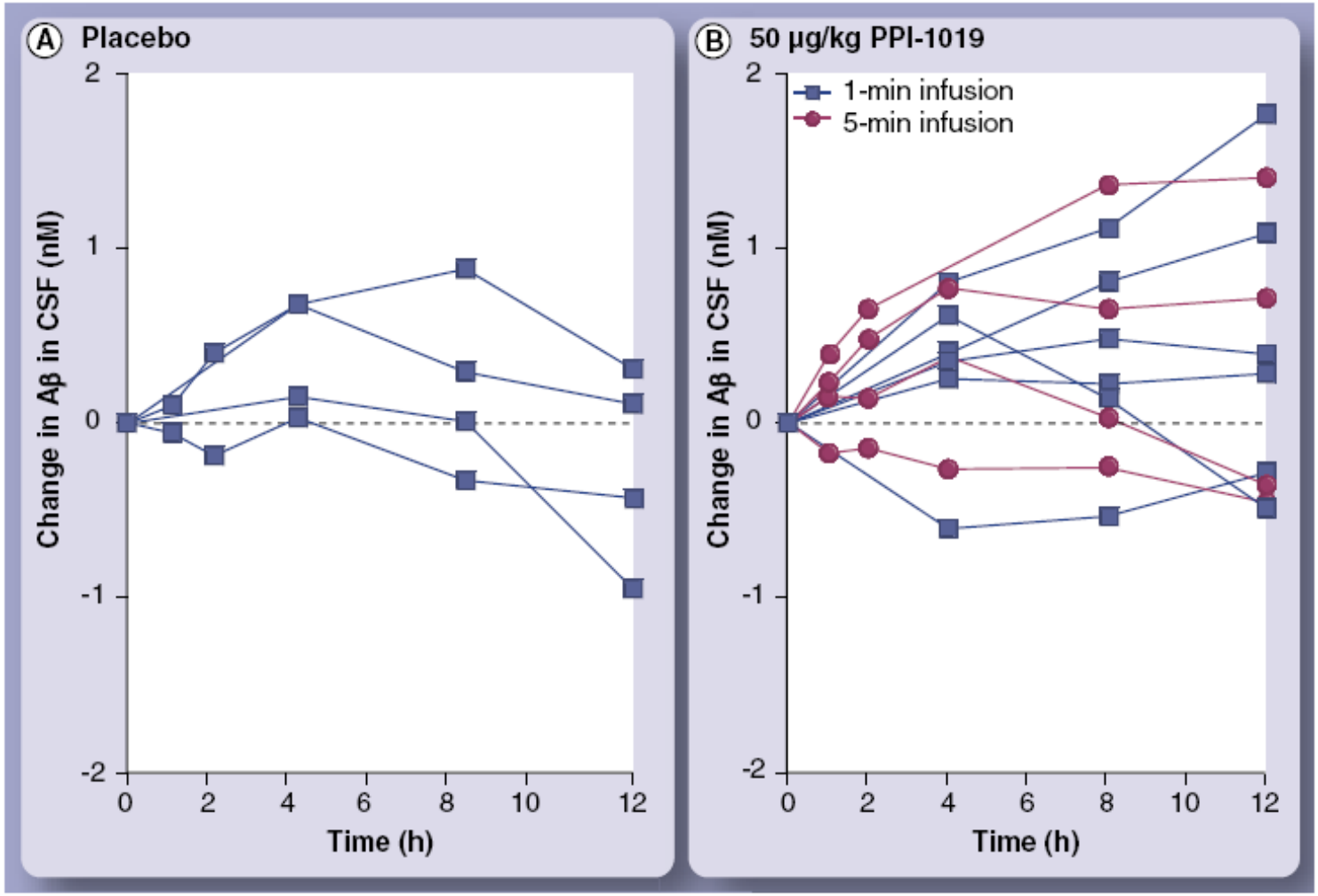

Figure 3. Change from baseline in cerebrospinal fluid amyloid-β.
Aβ: Amyloid-β; CSF: Cerebrospinal fluid.

Biomarkers Med. (2009) **3**(6), 711–721

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Context for Today's Session: Amyloid Modifying Drugs

- Given the dose - effect relationship on Aβ, can there be 'too much of a good thing"? i.e., cognitive worsening
- γ secretases have 'unwanted' effects, i.e., NOTCH
  - AE's include dermatological and GI symptoms, neoplasms, and immune dysfunction
- Potentially drugs affecting the amyloid cascade can result in CNS inflammatory changes and microhemorrhages
  - Recently: Ophthalmological/Retinal Monitoring
- There are dozens of substrates cleaved by gamma secretase
  - Potential toxicity beyond NOTCH? Are we targeting the best target in the amyloid cascade
  - BACE1 v. GSIs v. monoclonal antibodies v. modulators

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Context for Today's Session: Clinical Challenges

- What are the explanations for the disappointing results to date?
- When in the course of the illness is amyloid cascade modulation clinically relevant?
  - Once tau accumulation occurs, is it too late?
  - Down-stream and up-stream effects trigger neuronal metabolic and structural/functional changes
- Clinical trials methodology, patient selection, and use of correct scales
- Start to develop new approaches and 'solutions'
- Is amyloid burden 'lowering' (assuming safety can be achieved) a sufficient claim to allow a drug to be marketed?