

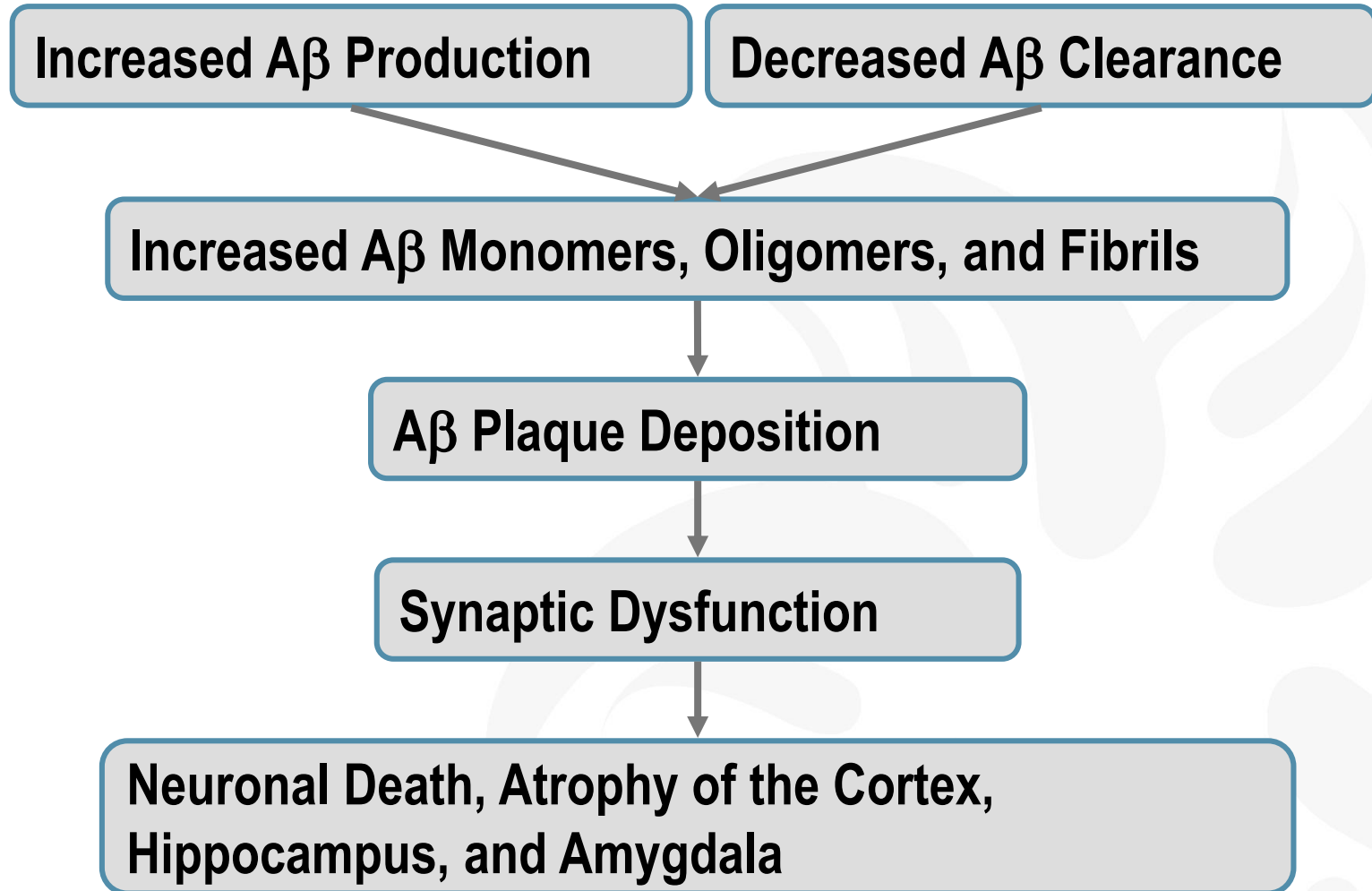
How Molecules that Fail Can Influence Future Research: Semagacestat and BACE Inhibitors

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Amyloid Cascade Hypothesis



Adapted from: Lichtlen P, Mohajeri MH. *J Neurochem*. 2008;104(4):859-874.
Parameshwaran K, et al. *Exp Neurol*. [Epub ahead of print].
Evin G, et al. *CNS Drugs*. 2006;20(5):351-372.

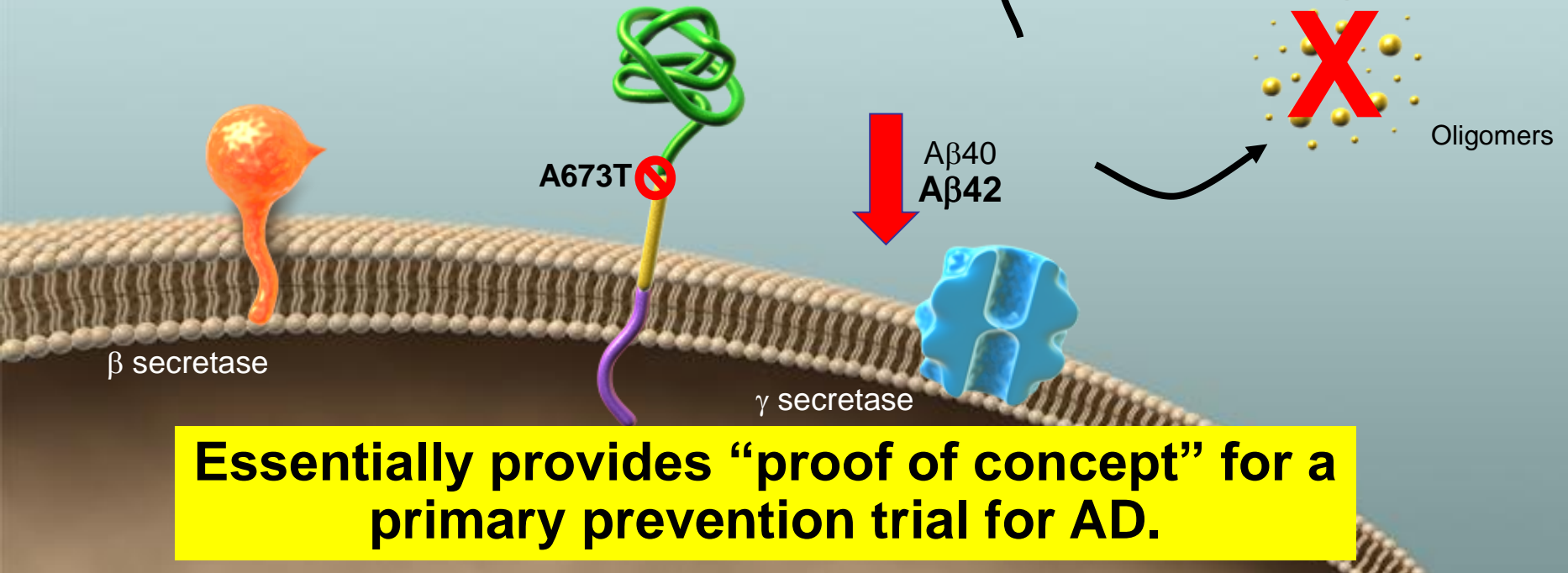
Genetic Support for Amyloid Hypothesis: *APP* (A673T) variant partially blocks *BACE* cleavage, reduces $A\beta$ production and prevents Alzheimer's Disease

LETTER

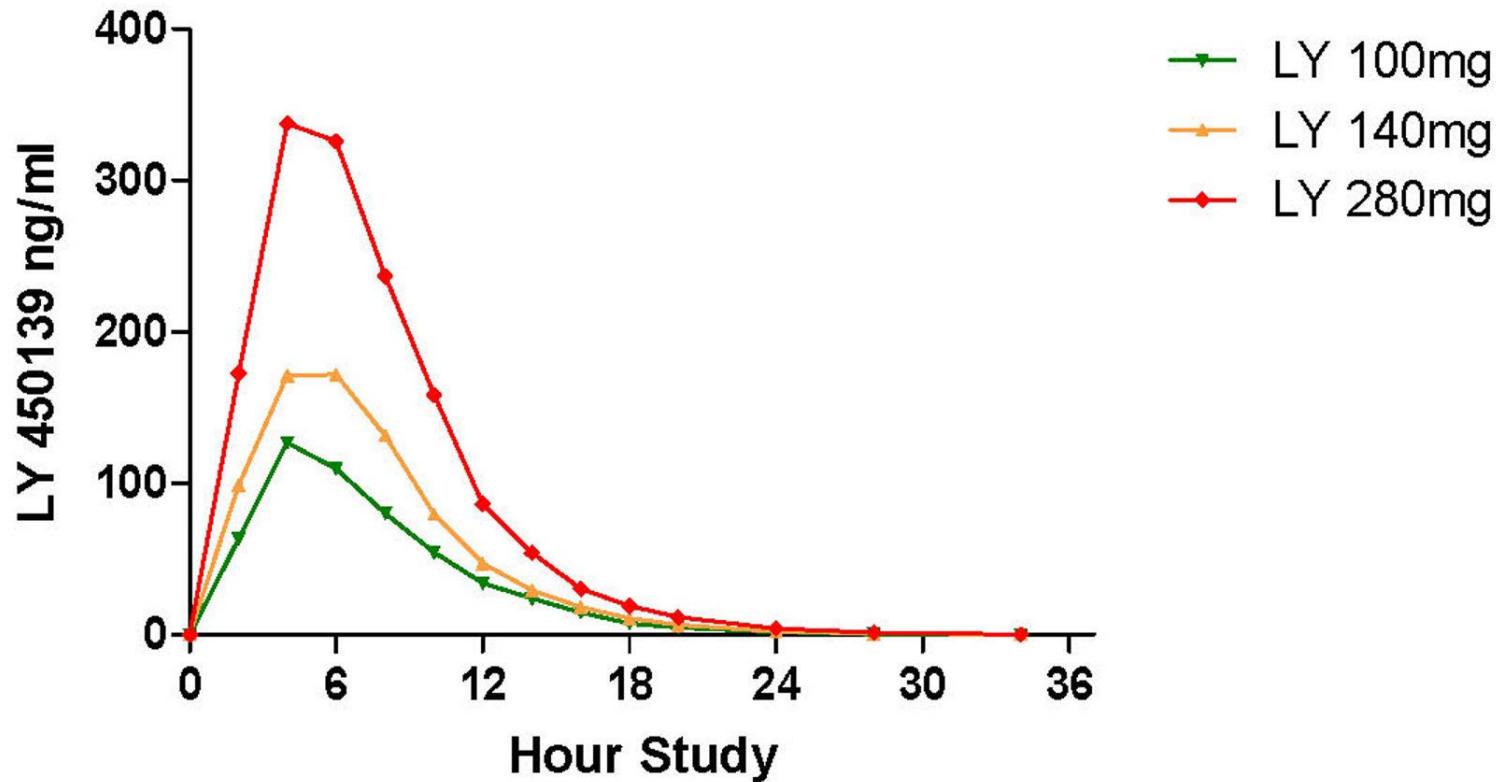
doi:10.1038/nature11283

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

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GSI-Semagacestat Showed Dose-Related Decrease CSF A-beta Production in Humans



From: Bateman et al. AnnNeurol, 2009.

Semagacestat Worsened both Cognition and Function in Phase 3

Table 2. Estimated Mean Change from Baseline for the Coprimary and Secondary Outcomes, According to a Mixed-Model Repeated-Measures Analysis.*

Outcome	Placebo	Semagacestat, 100 mg	Semagacestat, 140 mg	P Values	
				Sema- gacestat, 100 mg, vs. Placebo	Sema- gacestat, 140 mg, vs. Placebo
ADAS-cog score				0.15	0.07
No. of participants with results	486	483	497		
Mean change in score (95% CI)	6.4 (5.48 to 7.40)	7.5 (6.44 to 8.53)	7.8 (6.72 to 8.85)		
ADCS-ADL†				0.14	<0.001
No. of participants with results	480	481	490		
Mean change in score (95% CI)	-9.0 (-10.37 to -7.67)	-10.5 (-11.94 to -9.07)	-12.6 (-14.1 to -11.2)		

From: Doody et al. NEJM, 2013.

Semagacestat Also Produced Significant Non-CNS Side Effects

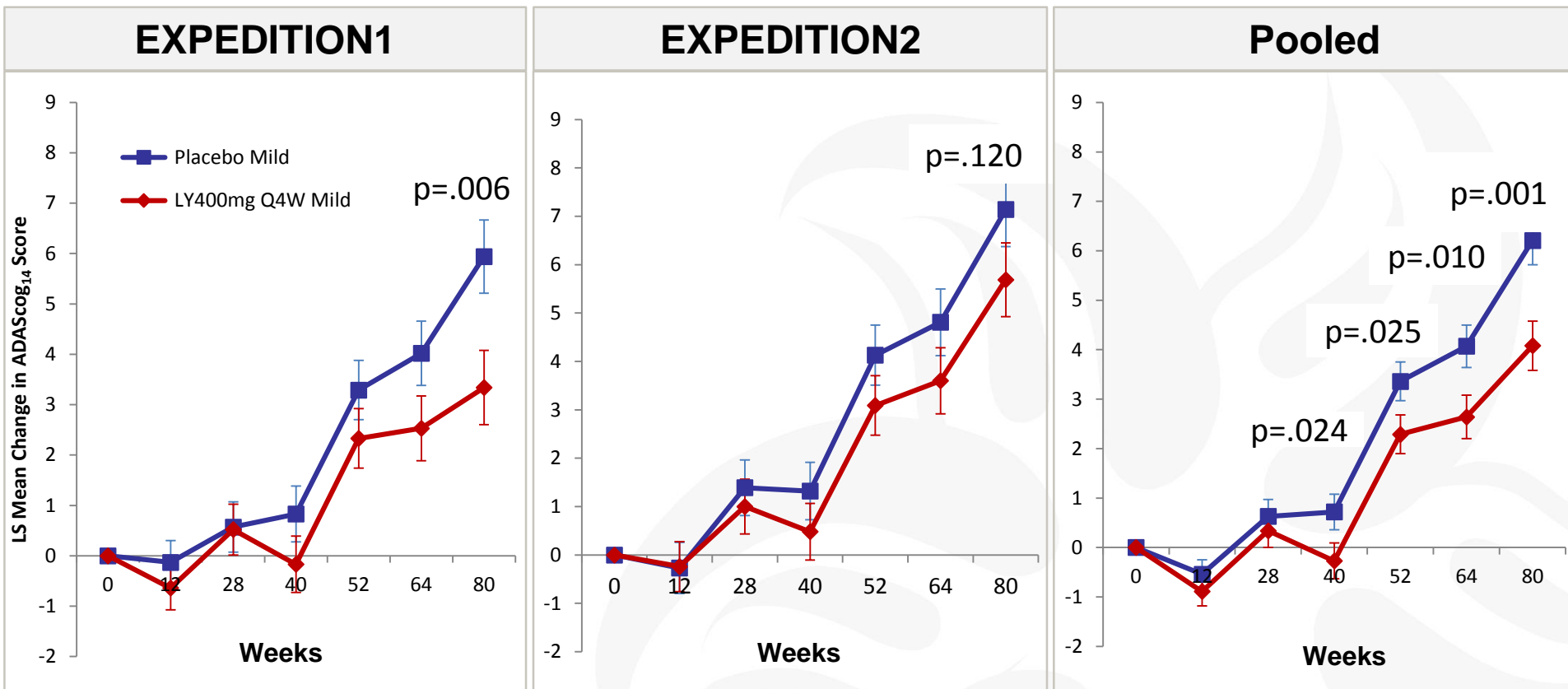
Table 3. Summary of Adverse Events Occurring during the Study Treatment, According to the MedDRA System or Organ Class and Preferred Term.*

Event	Placebo (N = 501)	Semagacestat			Total (N = 1534)
		100 mg (N = 506)	140 mg (N = 527)	Combined (N = 1033)	
<i>percent of participants</i>					
System or organ class					
Neoplasms — benign, malignant, or unspecified	5	15	16	15	12
Skin or subcutaneous-tissue disorders	21	45	52	48	39
Preferred term					
Alopecia	0	1	5	3	2
Basal-cell carcinoma	1	3	5	4	3
Decreased appetite	3	7	11	9	7
Epistaxis	1	3	3	3	2
Eyelash discoloration	0	2	5	3	2
Hair-color changes	1	13	19	16	11
Nausea	5	11	12	11	9
Pruritus	2	3	4	3	3
Rash					
Erythematous	2	5	5	5	4
Macular	4	7	8	8	6
Maculopapular	1	3	5	4	3
Papular	1	3	4	4	3
Skin lesion	1	3	3	3	2
Squamous-cell carcinoma of skin	1	6	5	5	4
Syncope	1	3	3	3	3
Vomiting	4	10	9	9	7
Weight decrease	3	5	9	7	6

Follow-Up from Semagacestat Experience

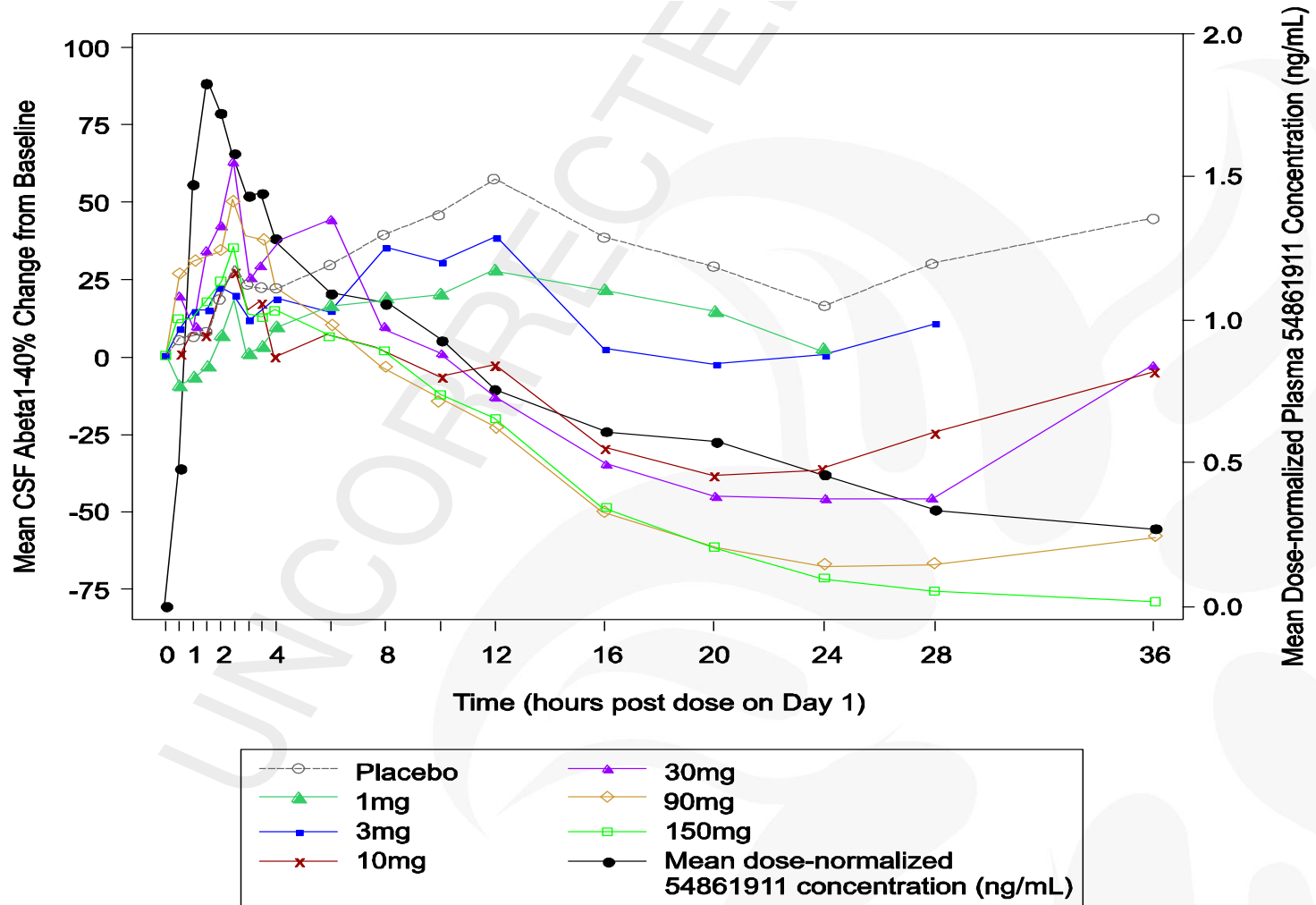
- Other GSI molecules showed similar results (e.g. BMS molecule)
- Substrates for GSI molecules other than α -beta (e.g. NOTCH) being investigated
- Little further development of GSI molecules for AD (GS Modulators still studied)
- Shift to development of BACE inhibitors and antibodies for AD
- GSI molecules may be useful in oncology (van Es et al. Nature, 2005) and otolaryngology (Hori et al. Neuroreport, 2007)

Solenazumab Showed Small Effect on Progression in EXPEDITION1, EXPEDITION2 and Pooled



Pooled analysis represented 34% slowing in cognitive decline at 80 weeks: EXPEDITION 3 showed non-significant slowing estimated at 11%; development discontinued.

BACE Inhibition May be Safer, More Potent Approach: Assays for A β Enable Dose Selection



BACE Inhibitors Continue in Development

- Some terminated due to Liver toxicity.
- Preclinical data warn of retinal problems. Need for eye exams in development programs.
- Potential skin problems. Need for skin exams in development programs.
- Remains to be determined whether these toxicities are mechanism related or off-target.
- Efficacy still uncertain but multiple programs ongoing.

Trends Following Sema, Sola, Other Antibody and BACE Results

- Ongoing studies will be completed
 - ◆ BACE Inhibitors
 - ◆ Other antibodies
 - ◆ Symptomatic agents
- Complimentary Mechanisms will be Emphasized
 - ◆ More potent antibodies
 - ◆ GS Modulators
- Different Mechanisms will be Emphasized
 - ◆ Anti-tau agregants
 - ◆ Anti-inflammatories
 - ◆ Symptomatic agents
- Smaller/less expensive POC studies will be more preferred
 - ◆ EPAD-Like studies
 - ◆ Study economics will be key

Improvements and Questions on Methodology

- Improvements

- Biological Homogeneity improved by amyloid imaging, CSF biomarkers (a-beta, tau), and genetic risk (APOE genotype)
- Natural history data enables sample size estimates (ADNI, others)
- Outcome measures for cognition, function, psychiatric symptoms and global
- PD biomarkers (plasma and CSF) for compounds targeting a-beta and tau

- Lingering Questions

- Stage of disease to target, dementia, prodromal, preclinical
- Matching outcomes to disease stage
- Can we do smaller, shorter studies that are informative?

Questions at Study Initiation

- Is the study informative even if the results do not show efficacy?
- Is it worth the cost if the results are negative?
- Can the scientific question be answered at less cost?
- Will the results of the study inform future studies, regardless of outcome?