Unexpected results from a γ-secretase inhibitor for Alzheimer's Disease: Implications for the amyloid hypothesis

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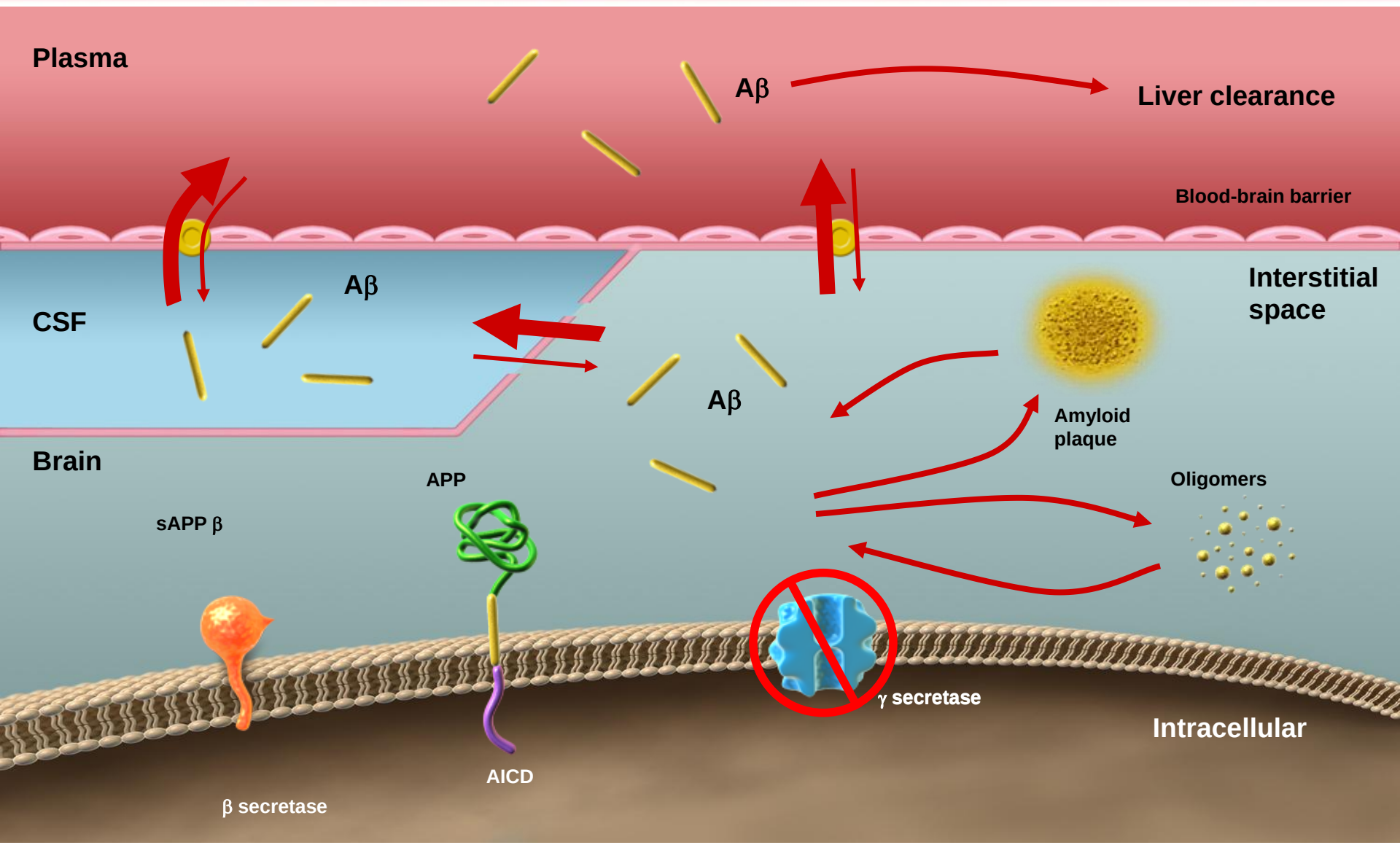
Lilly
Answers That Matter.

γ Secretase Inhibition



CSF=cerebrospinal fluid.

Lilly Halts Development of Semagacestat for Alzheimer's Disease Based on Preliminary Results of Phase III Clinical Trials

INDIANAPOLIS, Aug 17, 2010 /PRNewswire via COMTEX News Network/ -- Eli Lilly and Company (NYSE: LLY) will halt development of semagacestat, a gamma secretase inhibitor being studied as a potential treatment for Alzheimer's disease, because preliminary results from two ongoing long-term Phase III studies showed it did not slow disease progression and was associated with worsening of clinical measures of cognition and the ability to perform activities of daily living.

The company's decision does not affect the ongoing clinical trials of solanezumab, Lilly's other compound in Phase III trials as a potential Alzheimer's treatment. While both drugs focus on amyloid-beta proteins, which are believed to play a critical role in Alzheimer's disease, they have different mechanisms of action. Lilly also has two other compounds in earlier stages of clinical development; those studies are not affected by today's announcement.

In two pivotal Phase III trials, semagacestat was compared with placebo in more than 2,600 patients with mild-to-moderate Alzheimer's disease. Lilly has now reviewed data from a pre-planned interim analysis of semagacestat studies. This interim analysis showed that, as expected, cognition and the ability to complete activities of daily living of placebo-treated patients worsened. However, by these same measures, patients treated with semagacestat worsened to a statistically significantly greater degree than those treated with placebo. In addition, data showed semagacestat is associated with an increased risk of skin cancer compared with those who received placebo.

"This is disappointing news for the millions of Alzheimer's patients and their families worldwide who anxiously await a successful treatment for this devastating illness," said Jan M. Lundberg, Ph.D., Executive Vice President, Science and Technology, and President, Lilly Research Laboratories. "This is a setback, but Lilly's commitment to beating Alzheimer's will not waver."

Phase 2/3 data from Aβ-related compounds

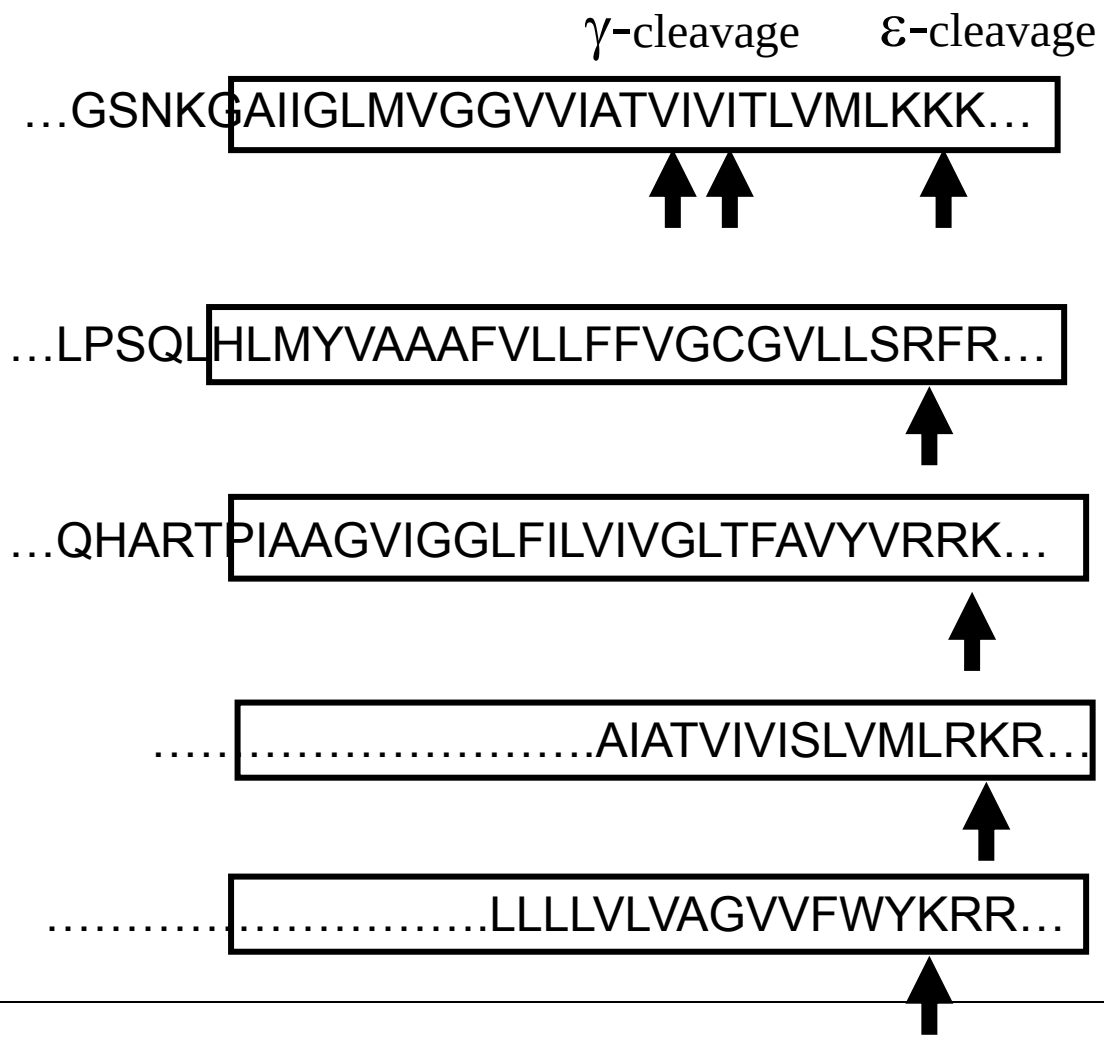
	Solanezumab (Lilly)	Bapineuzumab (Pfizer/JNJ)	Semagacestat (Lilly)	Flurbiprofen (Myriad)	Tramiprosate (Neurochem)	AN1792 (Elan/Wyeth)
Effect on Aβ/plaque	Monoclonal antibody (binds to mid-domain/ soluble Aβ)	Monoclonal antibody (binds to N-terminal/ plaque	γ-secretase inhibitor	γ-secretase modulator	Aβ anti-aggregating agent	Active immunization ($Aβ_{1-42}$/ adjuvant)
Pre-clinical change in plasma Aβ	Marked increase	N/A	60% reduction	≤50% reduction	N/A	N/A
Efficacy in Tg mouse chronic studies	Yes	Yes	Yes	Yes	Yes	Yes
Human plasma Aβ change	Marked increase	N/A	~70% reduction	N/A	N/A	N/A
Additional human biomarker changes	--Plasma Aβ change correlated to amyloid imaging --Plaque-specific Aβ species increased in plasma and CSF --Increase in CSF free $Aβ_{1-42}$	--attenuation in brain volume loss correlating with clinical change in Apo ε4 non-carrier sub-group (Phase 2 data) -- PIB reduction after 18 months	--Decrease in CSF Aβ concentration --Decrease in Aβ synthetic rate -- Increased alpha cleavage fragments	N/A	Disputed change in CSF Aβ concentration	--loss of brain volumes in responders --decrease in CSF tau concentration --reduction in plaque load with patho-logical examination
Potential safety concerns	Fc mediated (not seen in Phase 2)	Micro-hemorrhage/ focal brain edema	Notch related ?QTc prolonged CYP induction	Specificity for Aβ versus Notch	N/A	Meningo-encephalitis
Status	Phase 3 ongoing	Phase 3 ongoing	Stopped (worse cognition in Phase 3)	Stopped (lack of efficacy in Phase 3)	Stopped (lack of efficacy in Phase 3)	Stopped (safety in Phase 2)

Adapted from: Siemers ER, Dean RA, Demattos R, May PC. New Pathways in Drug Discovery for Alzheimer's disease. Curr Neurol Neurosci Rep 2006;6:372-378.

AD drugs that have failed in Phase 3

Drugs that failed	Drugs based on the amyloid hypothesis that failed	Drugs based on the amyloid hypothesis with robust Phase 2 biomarker data that failed
Atorvastatin/ simvastatin	Atorvastatin/ simvastatin	
Dimebon		
Flurbiprofen	Flurbiprofen	
Leuprolide		
Rosiglitazone		
Tramiprosate	Tramiprosate	
Xaliproden		
Semagacestat	Semagacestat	Semagacestat

Multiple substrates* for presenilin-dependent epsilon-cleavage of transmembrane proteins



APP
Yu et al., 2001
Gu et al., 2001
Sastre et al., 2001

mNotch1
Schroeter et al., 1998

Erb B4
Lee et al., 2002

rAPLP2
Gu et al., 2001

LRP
May et al., 2002

*Now over 50 presumptive substrates identified for gamma-secretase