[14:40 – 15:20]

Searching for blue ocean of Alzheimer's disease drug discovery

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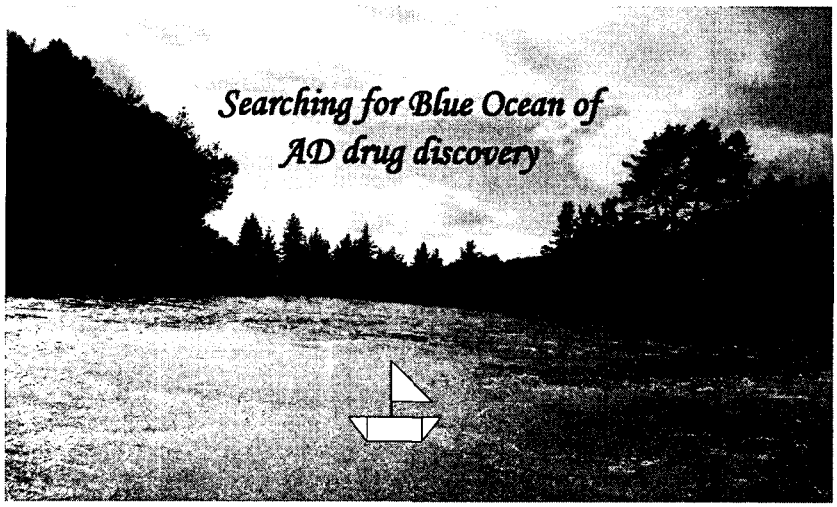
Alzheimer's disease (AD) is an age-related neurodegenerative disorder. The pathological hallmarks of AD are senile plaques and neurofibrillary tangles in the brain. Major component of senile plaques is amyloid beta peptide (Aβ) which is derived from amyloid precursor protein (APP). Aβ is generated through the sequential cleavage of APP by β- and γ-secretases. β-secretase excises the ectodomain of APP (β-APPs) to leave a 99-amino acid long C-terminal fragment (APP-C99-CTF) in the membrane. γ-secretase then cleaves this membrane-tethered APP-CTF within the transmembrane domain, so releasing Aβ peptides and APP-intracellular domain (AICD). Thus, β- and γ-secretase are regarded to perform the key steps in the pathogenesis of AD and have become important therapeutic targets in the prevention and treatment of AD.

Enormous efforts have been focused to develop the amyloid beta related drug for cure of AD becuase Aβ is believed to be one of the major causes of AD. Since major pharmaceutical companies in world wide base compete to develop new drug for AD, we have to be careful to choose the drug target to success the tough race.

In the present talk, possible drug targets based on basic research results will be discussed. These molecules should be a good target for development of new drug for AD and be less competitive to have a good shape for world wide competition.



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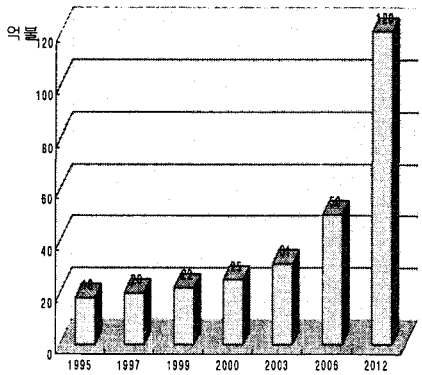
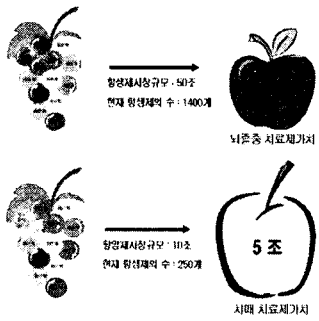
묵 인 희

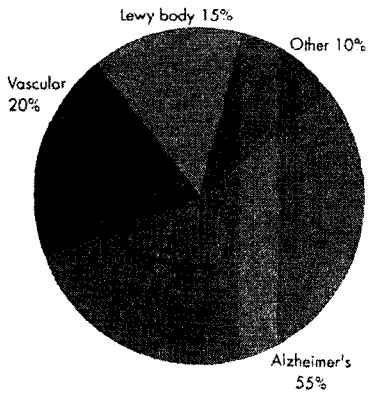
치매 치료제의 세계 시장





(자료원: IMS Health World Review. 1999. 4)

Dementia & Alzheimer's Disease



AD 환자수

미국 400 만명
세계 1,500 만명

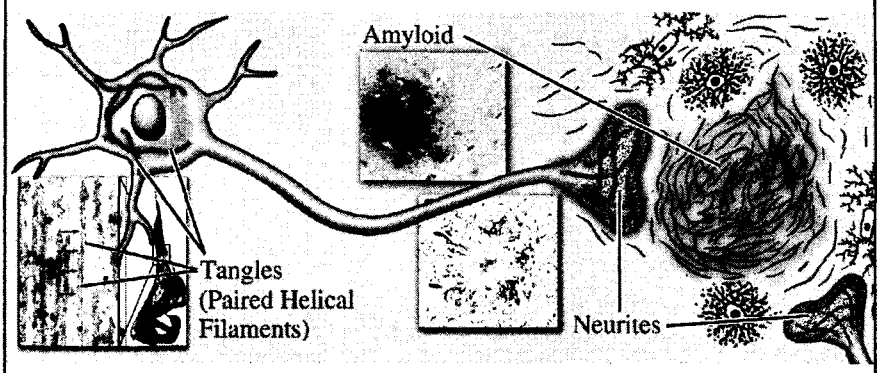
알츠하이머병 연구개발의 필요성

- 고령인구 증가에 따른 알츠하이머병 환자수의 급속한 증가
- 치료 및 예방 방법의 부재

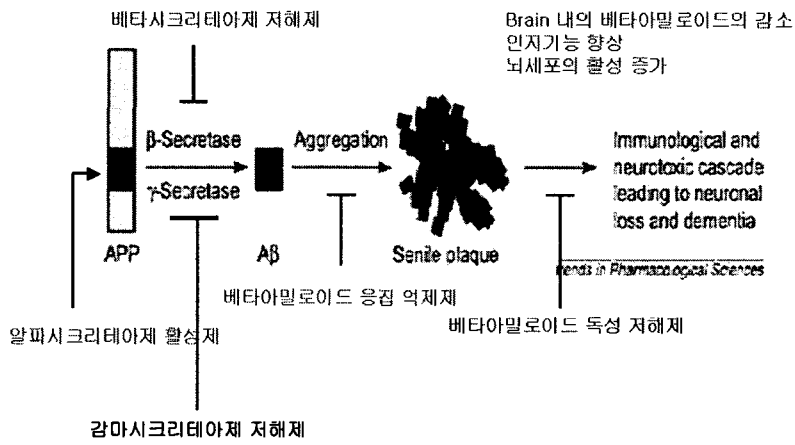
질병	전체 예상 환자수	의료비 지출/년
알츠하이머병	**5,000,000**	**100 billion dollar**
파킨슨병	1,000,000	5 - 10 billion dollar
Stroke	3,000,000	50 billion dollar
Spinal cord injury	500,000	5 billion dollar
Schizophrenia	1,500,000	40 billion dollar

(인용: 미국 NIH, Voluntary Organization, 1990 및 1997년 자료집; NINDS Congressional Report 2001)

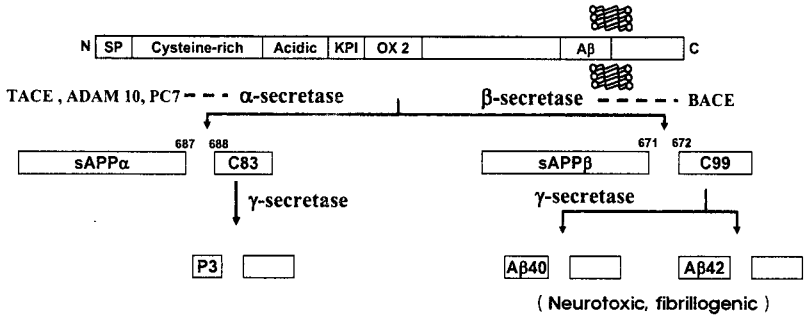
Pathology in Alzheimer's Disease



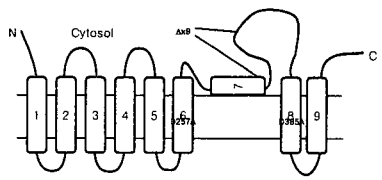
베타아밀로이드를 중심으로 하는 신약개발 목표점



Pathways of APP processing by α, β and γ-secretases



Schematic representation of PS1



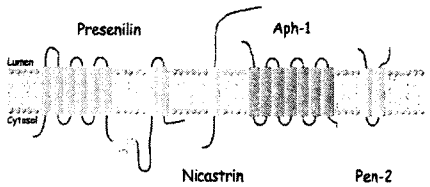
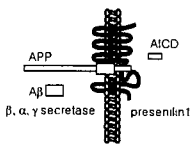
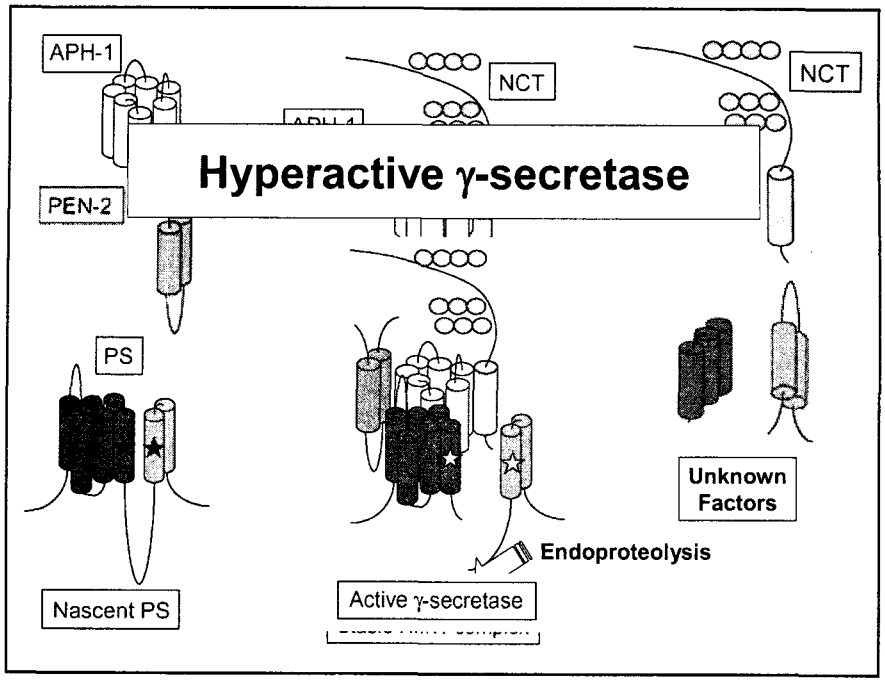
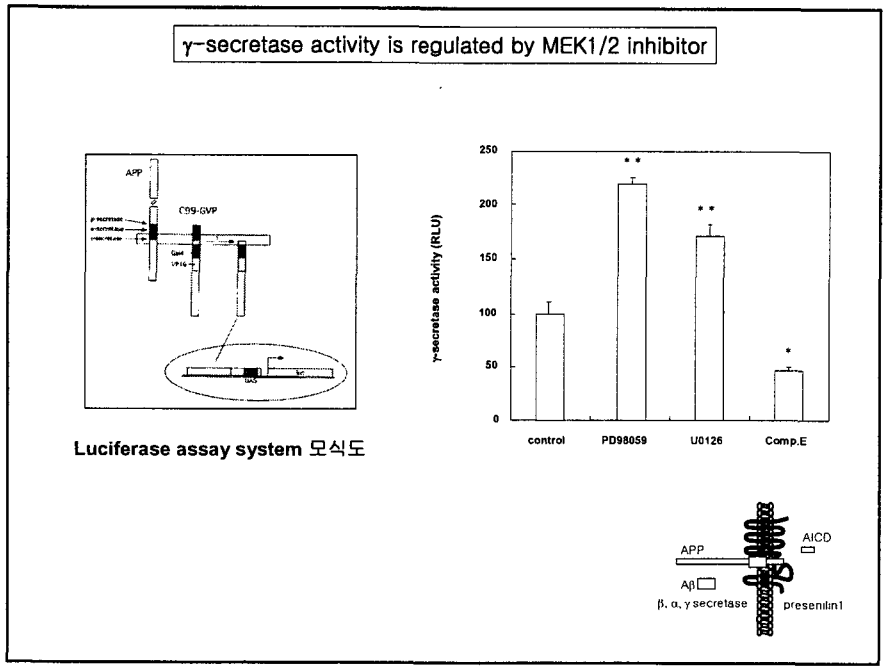
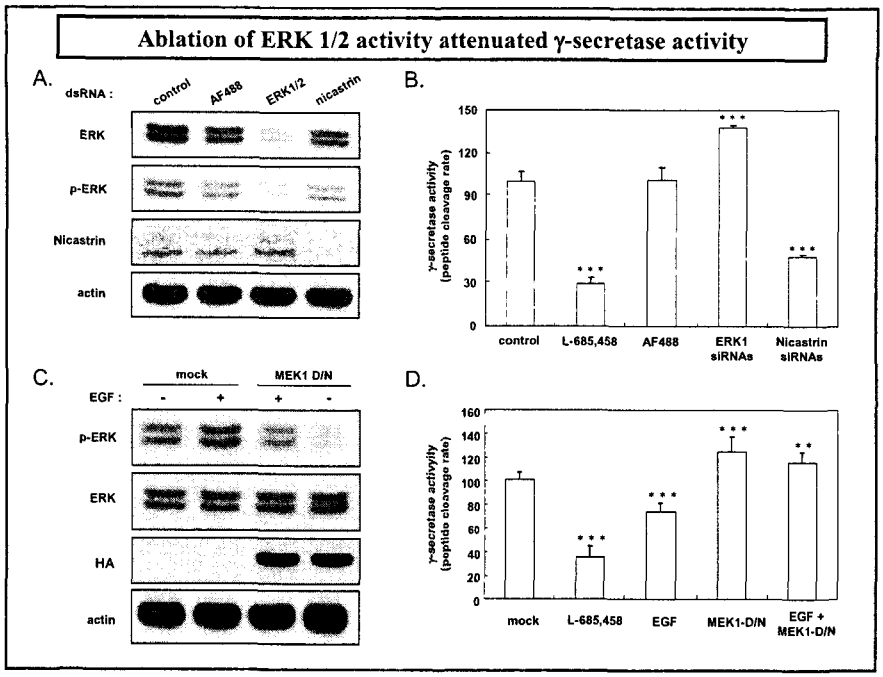


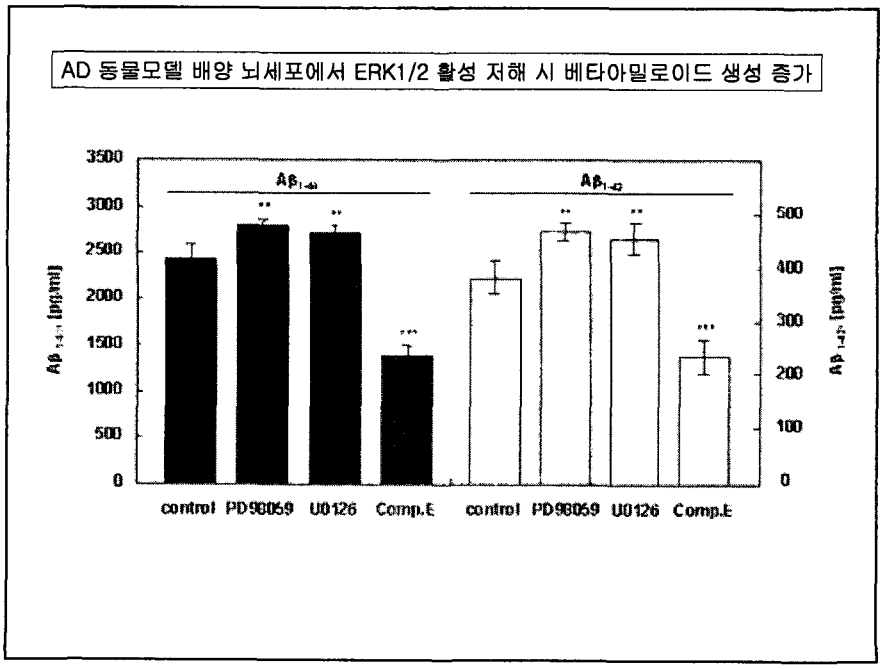
Figure 1. The Core of the γ-secretase Complex



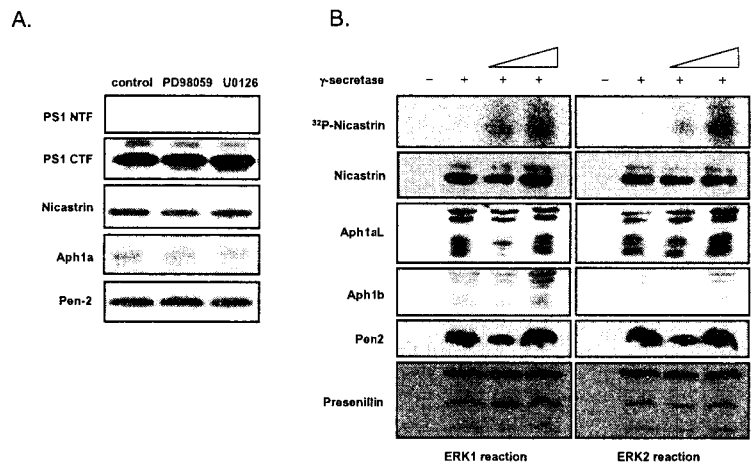

APH-1
NCT
NCT
Hyperactive γ-secretase
PEN-2
PS
Unknown Factors
Endoproteolysis
Nascent PS
Active γ-secretase


γ-secretase is regulated by MEK1/2 inhibitor
APP
C99-GVP
Luciferase assay system 모식도
γ-secretase activity (RLU)
250
200
150
100
50
0
control
PD98059
U0126
Comp.E
APP
AICD
Aβ
β, α, γ secretase
presenilin1

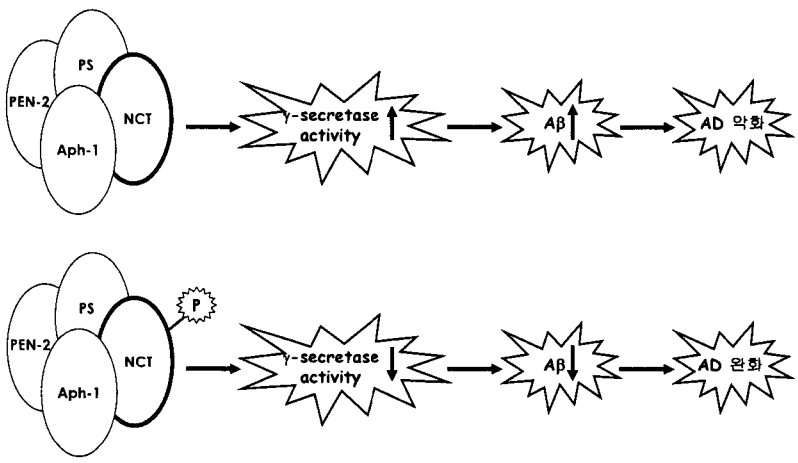

Ablation of ERK 1/2 activity attenuated γ-secretase activity
A.
dsRNA :
control
AF488
ERK1/2
nicastrin
ERK
p-ERK
Nicastrin
actin
B.
γ-secretase activity (peptide cleavage rate)
150
120
90
60
30
0
control
L-685,458
AF488
ERK1 siRNAs
Nicastrin siRNAs
C.
mock
MEK1 D/N
EGF :
- + + -
p-ERK
ERK
HA
actin
D.
γ-secretase activity (peptide cleavage rate)
160
140
120
100
80
60
40
20
0
mock
L-685,458
EGF
MEK1-D/N
EGF + MEK1-D/N

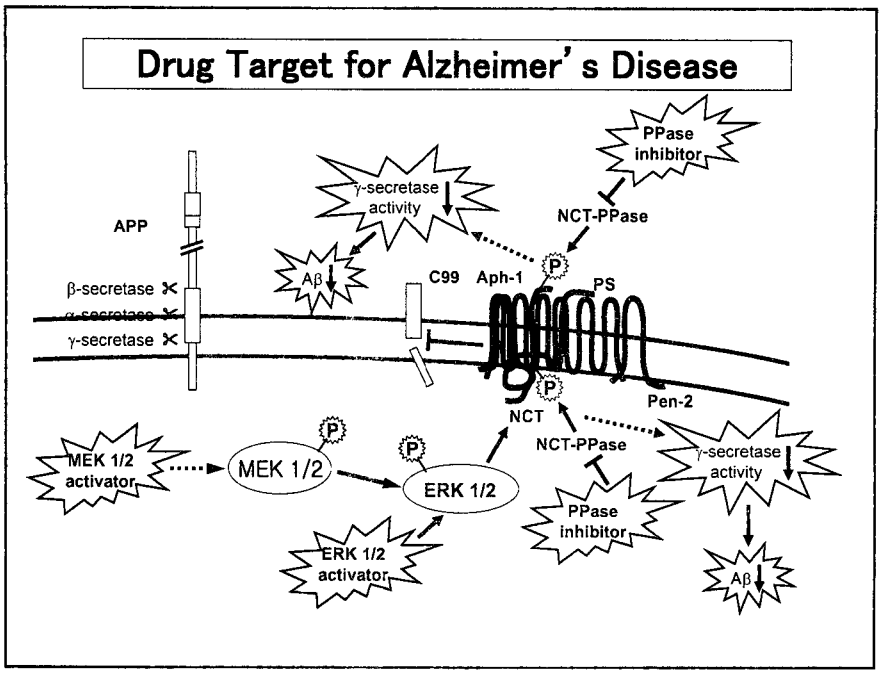

AD 동물모델 배양 뇌세포에서 ERK1/2 활성 저해 시 베타아밀로이드 생성 증가
3500
3000
2500
2000
1500
1000
500
0
500
400
300
200
100
0
control
PD98059
U0126
Comp.E
control
PD98059
U0126
Comp.E

ERK1/2 phosphorylated only nicastrin in γ-secretase complex



Drug Target for Alzheimer's Disease

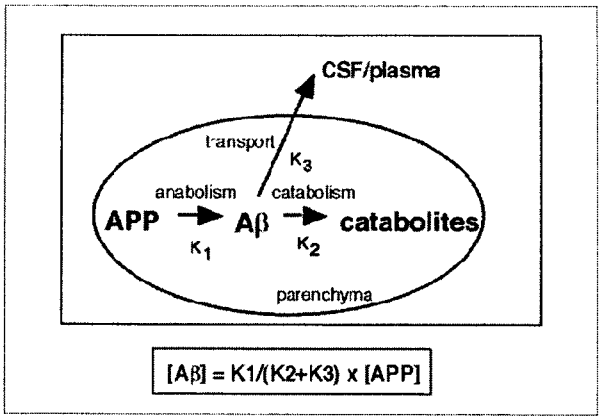




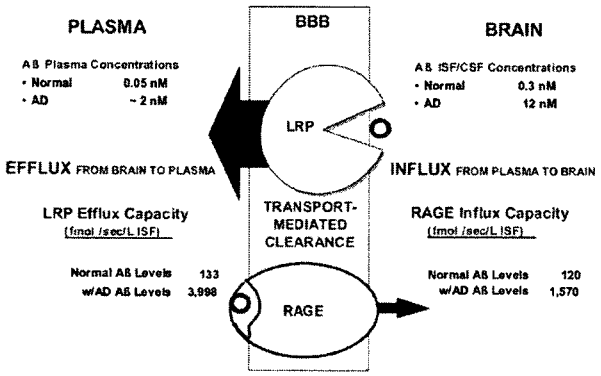
Drug Discovery Status of phosphatase inhibitors

기전	의약품명	개발회사	단계	대상질환	기타
Protein tyrosine phosphatase 1B inhibitor	Ertiprotafib	Wyeth	Phase II	Type II diabete	Benseneprop anoic acid
	ISIS-113715	ISIS Pharmaceuticals	Preclinical	Type II diabete Obesity	2nd generation antisense PTP-1B inhibitor
	OC-86839	Ontogen	preclinical	Type II diabete Obesity	Selective non-peptide PTP-1B inhibitor
	PTP1B inhibitor	Abbott	preclinical	Type II diabete Obesity	PTP-1B inhibitor
	PTP1B inhibitor	Array BioPharma	preclinical	Type II diabete Obesity	PTP-1B inhibitor
	PTP1B inhibitor	Structural Bioinformatics	preclinical	Type II diabete Obesity	Orally-active selective PTP-1B inhibitor
	PTP inhibitor	Kaken Pharmaceuticals	preclinical	Type II diabete Obesity	Orally-active PTP-1B inhibitor
	PTP inhibitor	AGY Therapeutics	preclinical	Alzheimer's disease Cognitive disorder	PTP inhibitor

Concentration of Aβ in the brain



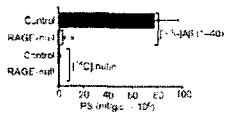
RAGE : Receptor for advanced glycation endproducts (AGEs)

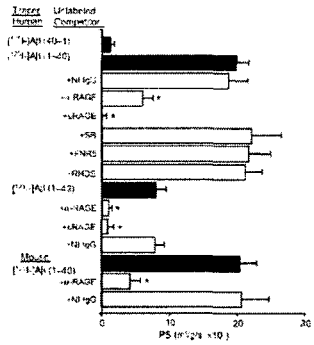


RAGE mediates amyloid-β peptide transport across the blood-brain barrier and accumulation in brain

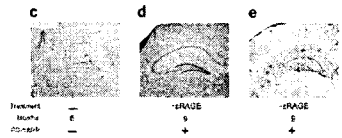
Nat Med. 2003 Jul;9(7):907-13.

RAGE-dependent BBB transport of circulating Aβ

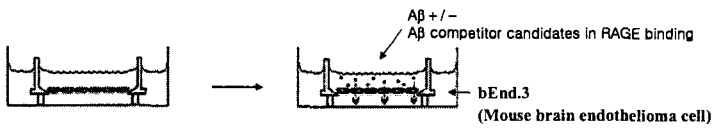




PD-hAPP mice treated with sRAGE or RAGE Ab promotes egress of Aβ from the CNS



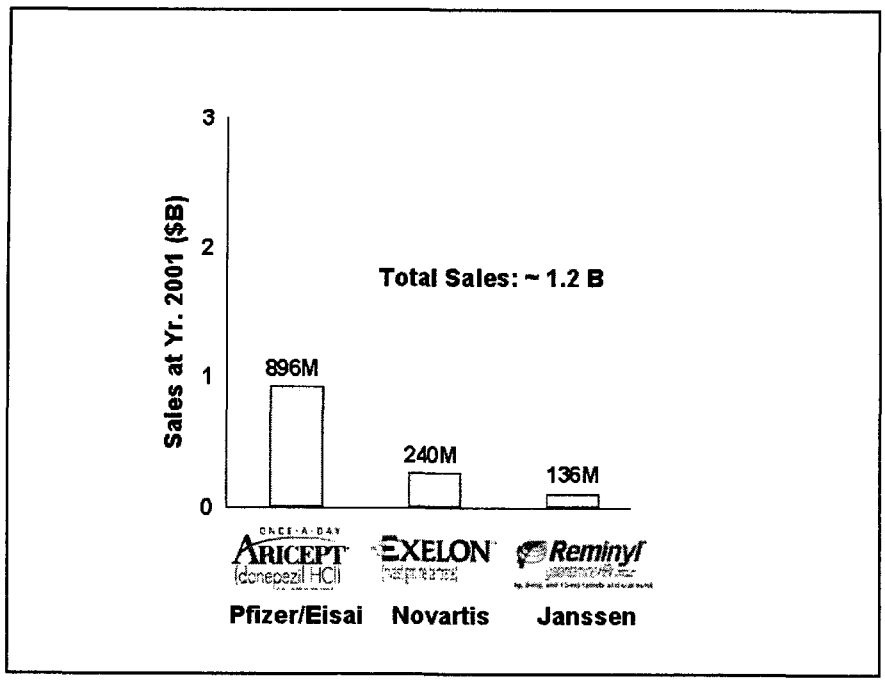
Investigation into natural competitors to Aβ in RAGE binding : using the in vitro model of BBB

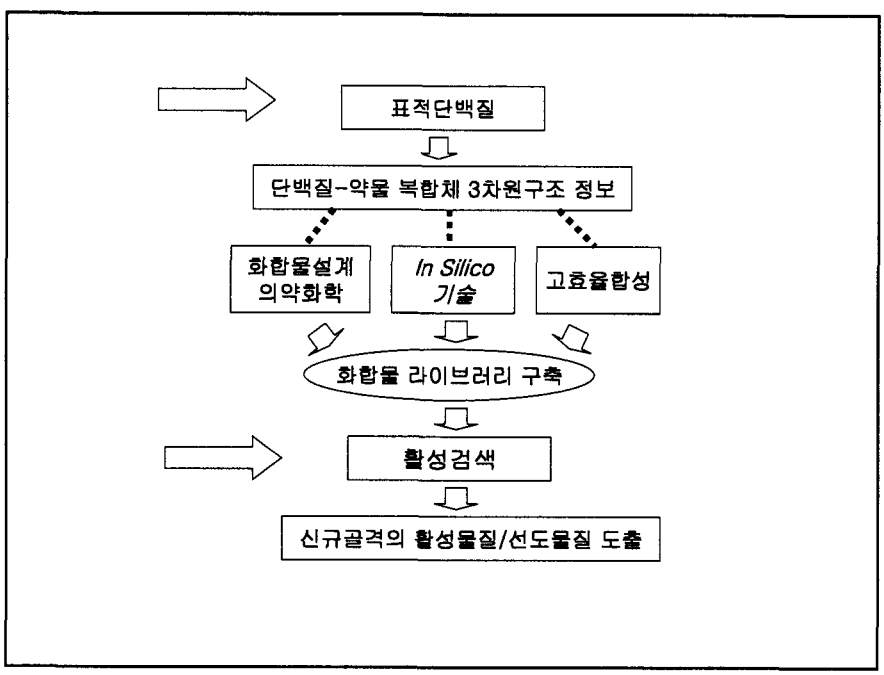


brain endothelial cell monolayer maintenance phase

permeability test of the reference molecule or drug candidates (dextran-FITC or Aβ-FITC)

Establishment a high quality in vitro BBB model in which experiments with physiological, pharmacological and pathophysiological objectives can be reproducibly performed


Sales at Yr. 2001 ($B)
3
2
1
0
Total Sales: ~ 1.2 B
896M
240M
136M
ARICEPT
(donepezil HCl)
EXELON
Reminyl
Pfizer/Eisai
Novartis
Janssen


표적단백질
단백질-약물 복합체 3차원구조 정보
화합물설계
의약화학
In Silico
기술
고효율합성
화합물 라이브러리 구축
활성검색
신규골격의 활성물질/선도물질 도출