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Searching for blue ocean of  
Alzheimer's disease drug discovery

Prof. Inhee Mook-Jung  
(*Seoul National University*)



[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 ( $A\beta$ ) which is derived from amyloid precursor protein (APP).  $A\beta$  is generated through the sequential cleavage of APP by  $\beta$ - and  $\gamma$ -secretases.  $\beta$ -secretase excises the ectodomain of APP ( $\beta$ -APPs) to leave a 99-amino acid long C-terminal fragment (APP-C99-CTF) in the membrane.  $\gamma$ -secretase then cleaves this membrane-tethered APP-CTF within the transmembrane domain, so releasing  $A\beta$  peptides and APP-intracellular domain (AICD). Thus,  $\beta$ - and  $\gamma$ -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 because  $A\beta$  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.

*Searching for Blue Ocean of  
AD drug discovery*

서울대학교 의과대학 생화학교실  
목인희

## 지매 치료제의 세계 시장

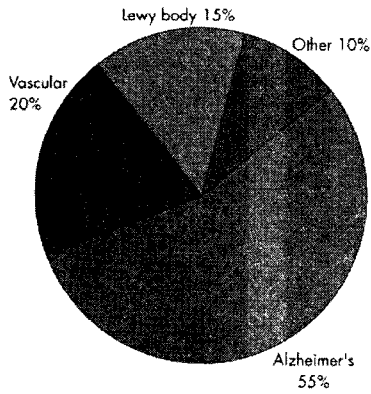
Year	Market Size (Billion Won)
1995	~25
1997	~28
1999	~32
2000	~35
2003	~42
2006	~58
2012	~125

상연제 시장 규모 : 50조  
 현재 항진제의 수 : 1400개  
 뇌졸중 치료제까지

상연제 시장 규모 : 10조  
 현재 항진제의 수 : 250개  
 5조  
 치매 치료제까지

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

## Dementia & Alzheimer's Disease



### AD 환자수

미국 400 만명  
세계 1,500 만명

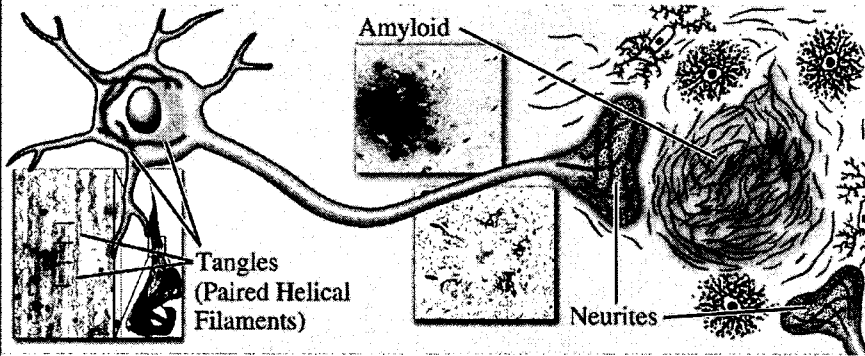
## 알츠하이머병 연구개발의 필요성

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

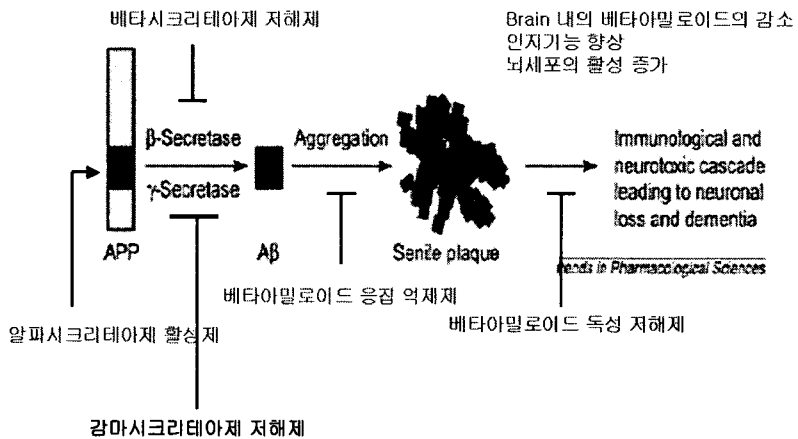
질병	전체 예상 환자수	의료비 지출/년
알츠하이머병	5,000,000	100 billion dollar
파킨슨병	1,000,000	5 - 10 billion dollar
Stroke	3,000,000	50 billion dollar
Spinal cord injury	500,000	5 billion dollar
Schizophrenia	1,500,000	40 billion dollar

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

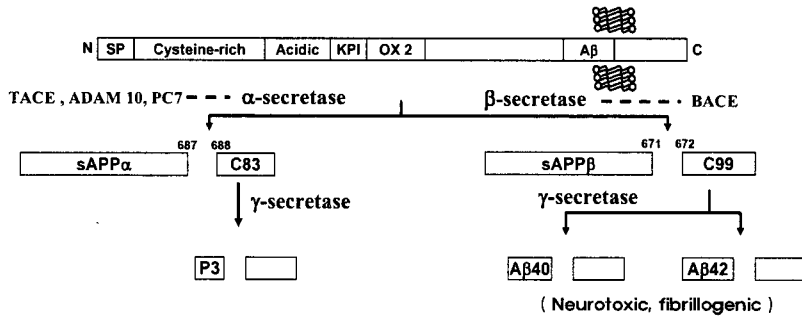
## Pathology in Alzheimer's Disease



### 베타아밀로이드를 중심으로 하는 신약개발 목표점



## Pathways of APP processing by $\alpha$ , $\beta$ and $\gamma$ -secretases



## Schematic representation of PS1

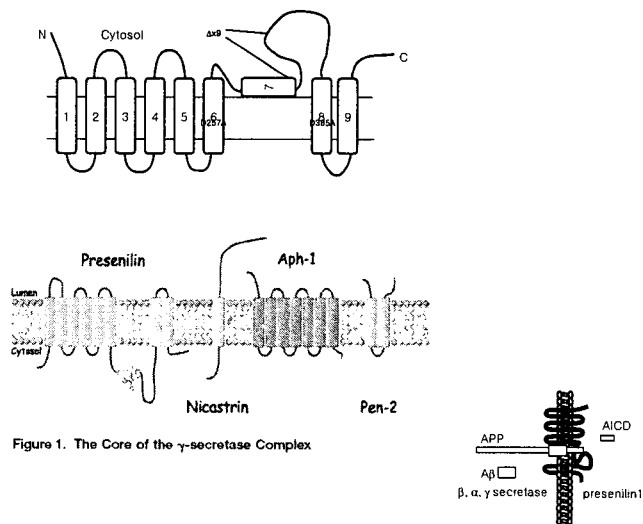
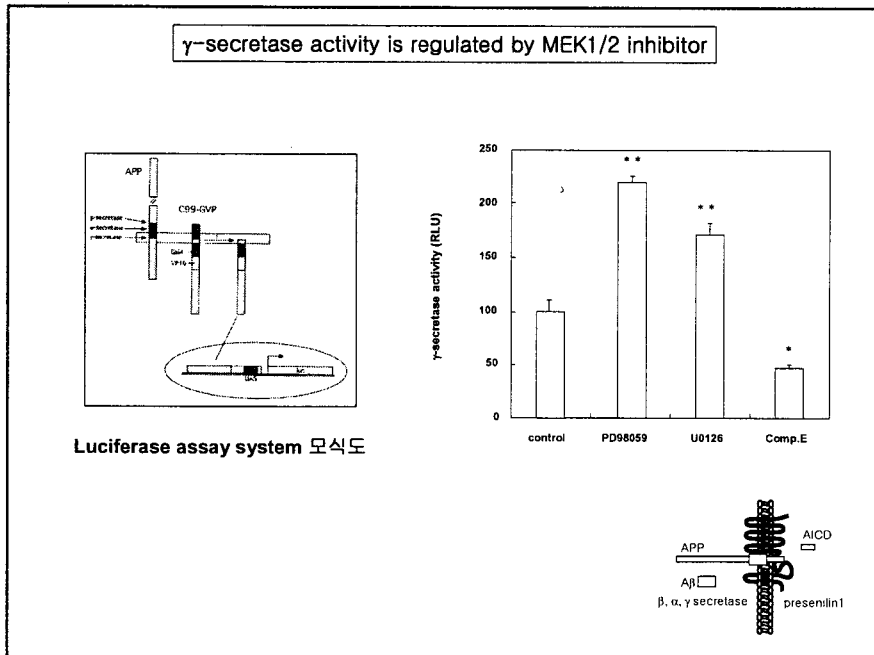
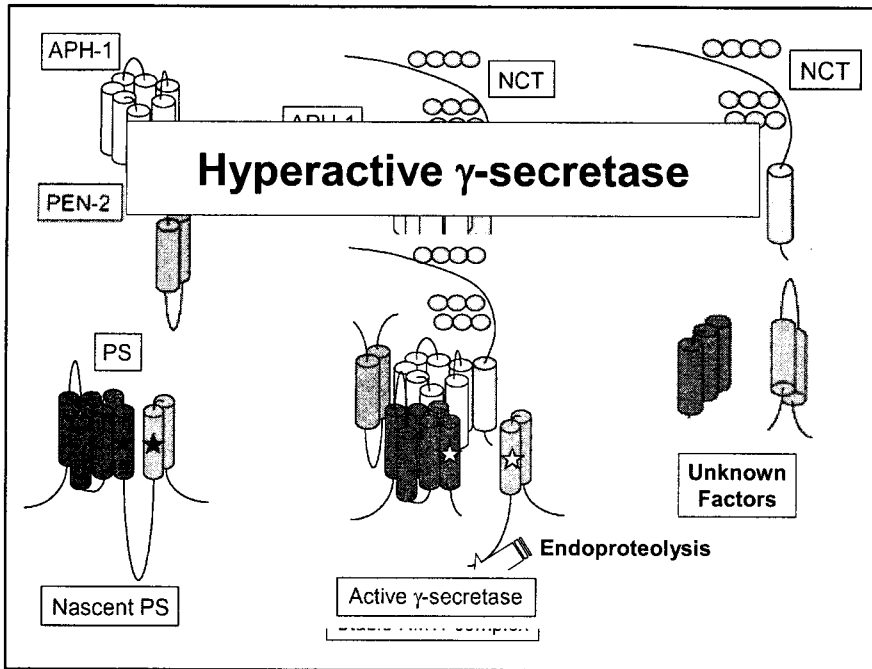
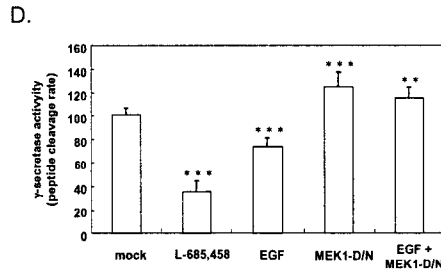
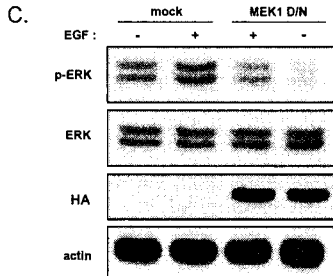
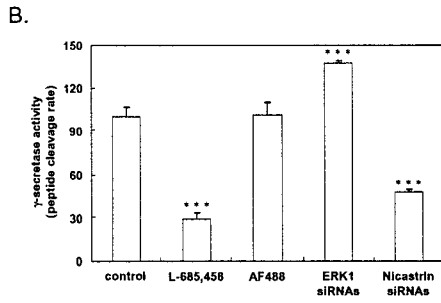
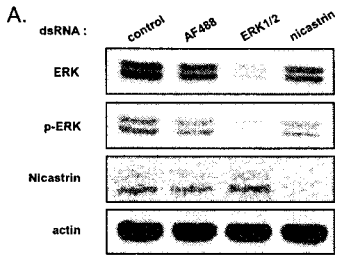


Figure 1. The Core of the  $\gamma$ -secretase Complex

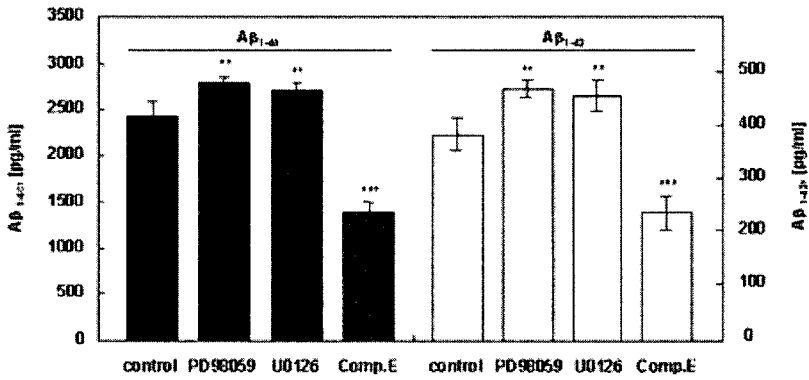




### Ablation of ERK 1/2 activity attenuated $\gamma$ -secretase activity

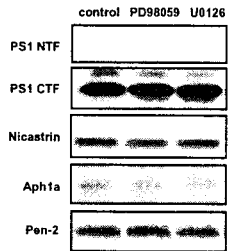


### AD 동물모델 배양 뇌세포에서 ERK1/2 활성 저해 시 베타아밀로이드 생성 증가

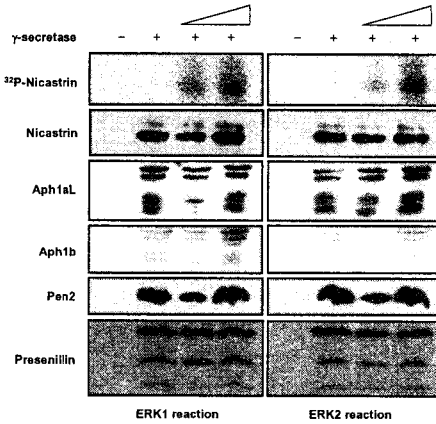


## ERK1/2 phosphorylated only nicastrin in $\gamma$ -secretase complex

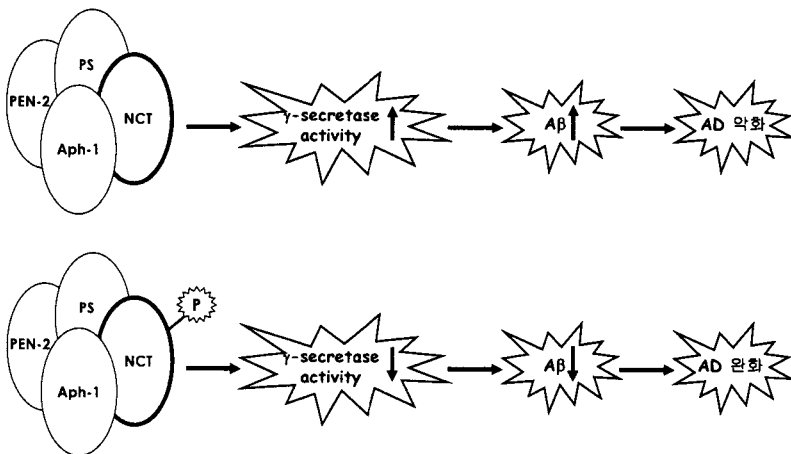
A.

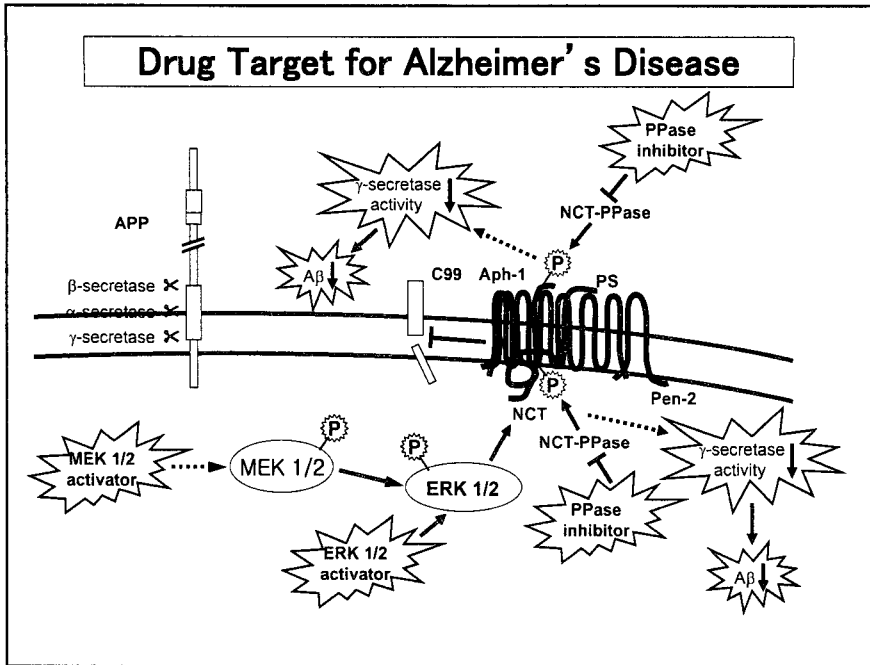


B.



## Drug Target for Alzheimer's Disease

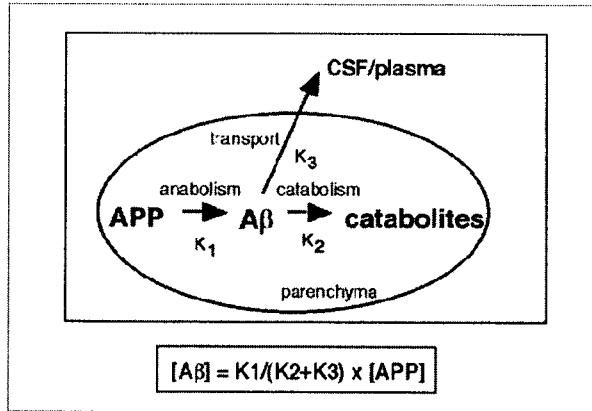




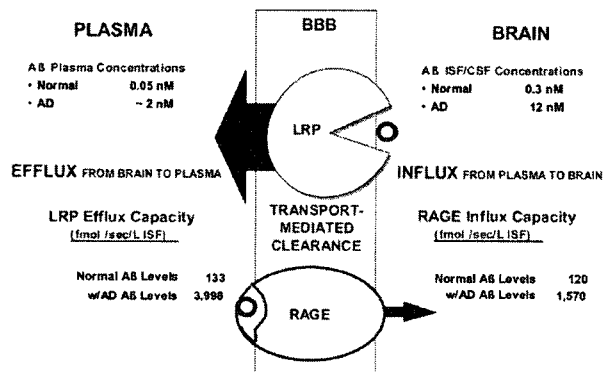
### Drug Discovery Status of phosphatase inhibitors

기전	의약품명	개발회사	단계	대상질환	기타
Protein tyrosine phosphatase 1B inhibitor	Ertiprotafib	Wyeth	Phase II	Type II diabete	Bensenepropanoic acid
	ISIS-113715	ISIS Pharmaceuticals	Preclinical	Type II diabete Obesity	2 <sup>nd</sup> generation antisense PTP-1B inhibitor
	OC-86839	Ontogen	preclinical	Type II diabete Obesity	Selective non-peptide PTP-1B inhibitor
	PTP1B inhibitor	Abbot	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 A $\beta$ in the brain



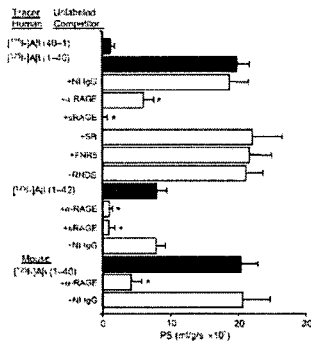
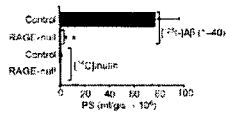
### RAGE : Receptor for advanced glycation endproducts (AGEs)



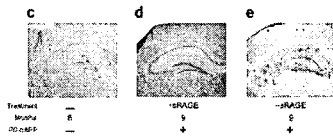
***RAGE mediates amyloid- $\beta$  peptide transport across the blood-brain barrier and accumulation in brain***

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

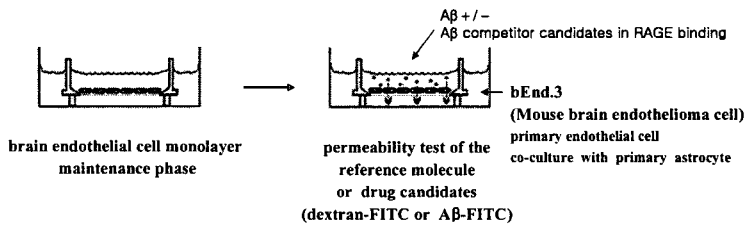
**RAGE-dependent BBB transport of circulating A $\beta$**



**PD-hAPP mice treated with sRAGE or RAGE Ab promotes egress of A $\beta$  from the CNS**



***Investigation into natural competitors to A $\beta$  in RAGE binding : using the in vitro model of BBB***



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

