2019. 11.26

반응성 별세포를 공략하여 치매 치료제를 개발하다!

Targeting Reactive Astrocytes to Develop Alzheimer Disease Drug.

이창준

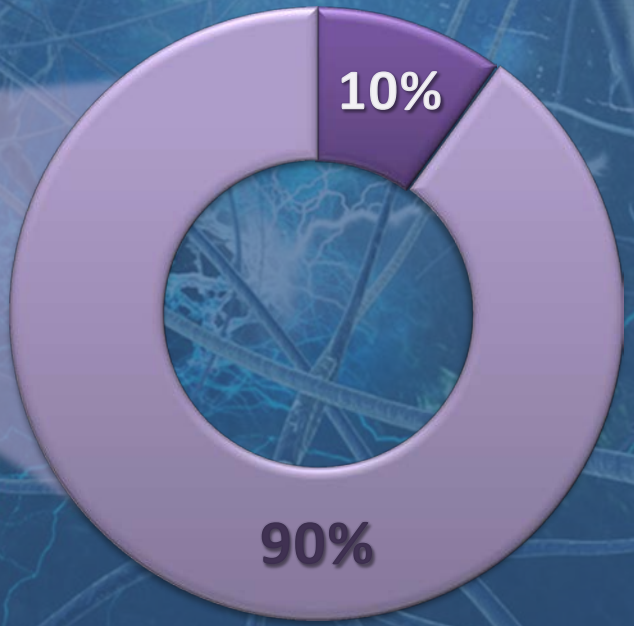
C. Justin Lee, PhD

Institute for Basic Science (IBS)

Center for Cognition and Sociality

Cognitive Glioscience Group

뇌의 대부분을 차지하는 신경교세포



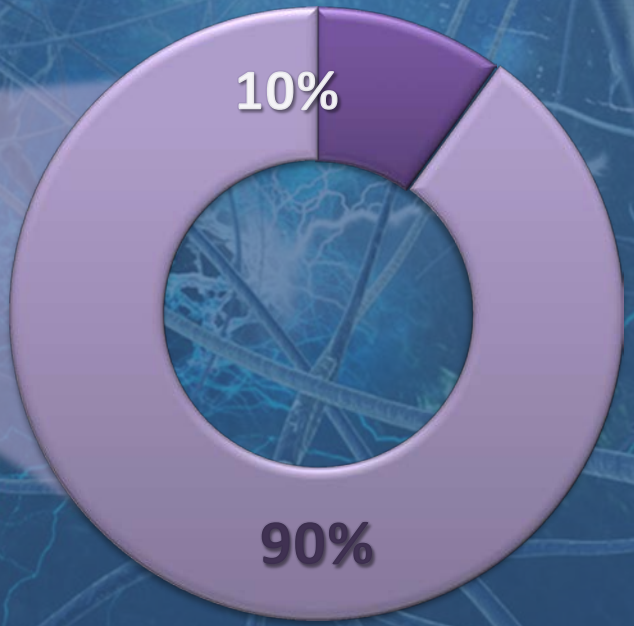
신경세포(Neuron)

신경교세포(glia)

뇌의 대부분을 차지하는 신경교세포

신호전달물질 분비 및
시냅스 신호전달

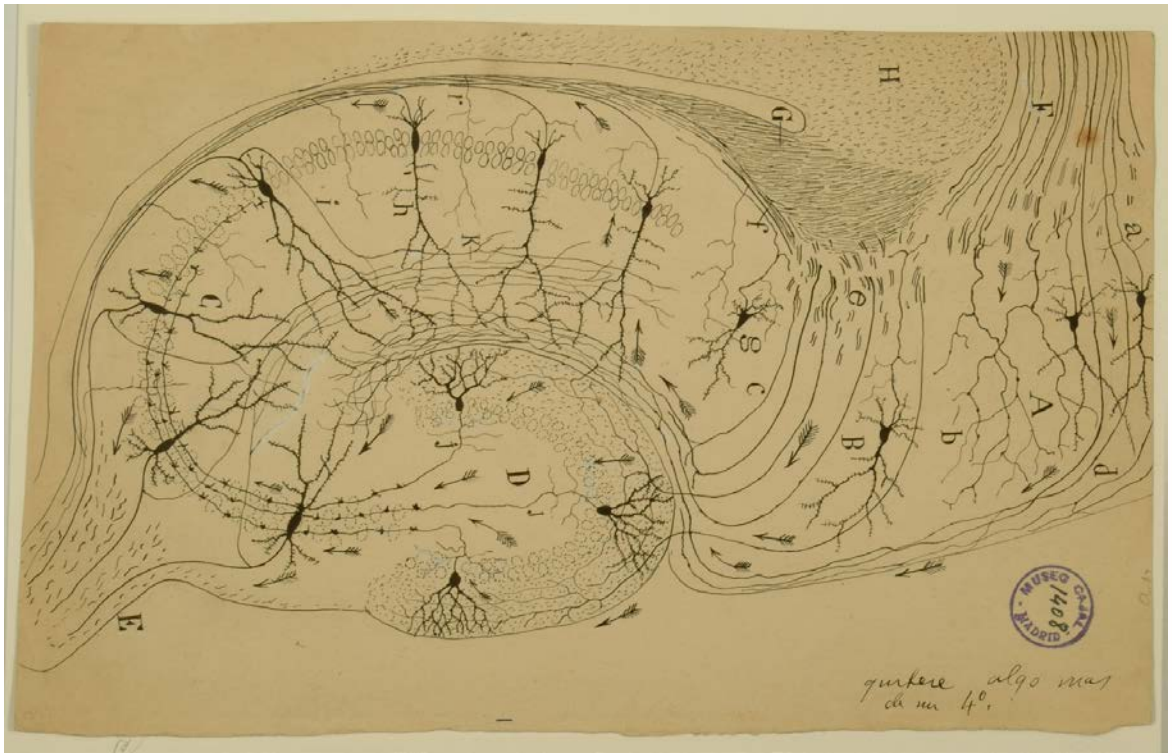
신경세포(neuron)



주위 청소 와 신경세포
보조

신경교세포(glia)

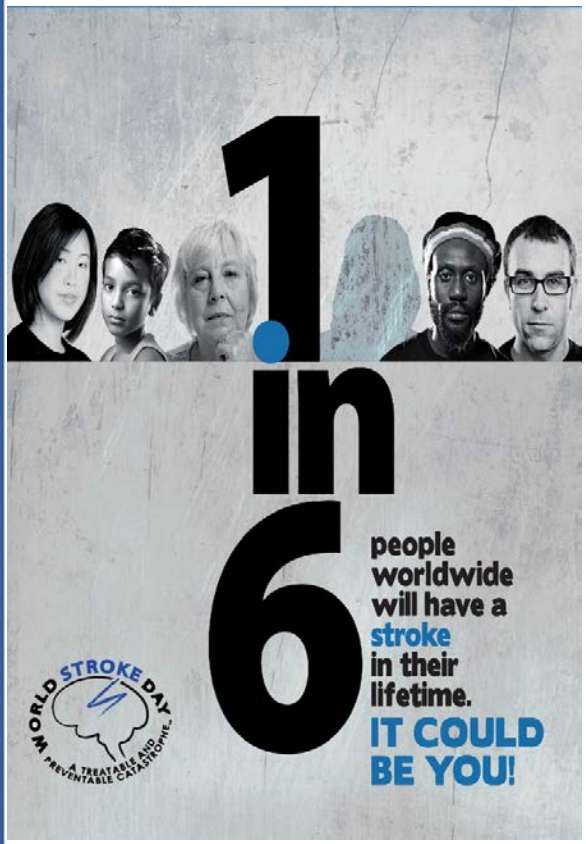
과학기술적/사회경제적 문제제기: 신경세포중심적인 뇌연구.



Santiago Ramón y Cajal : “The Neuron Doctrine”

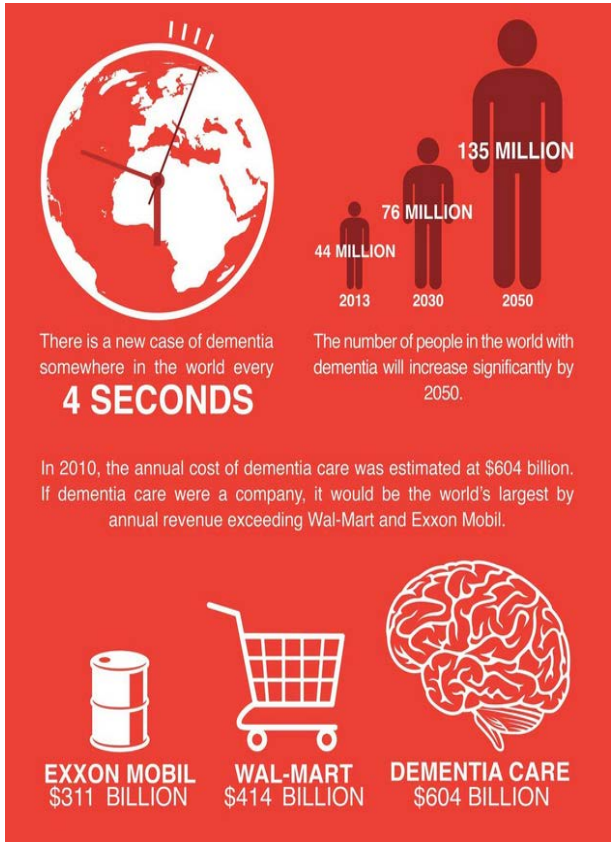
뇌 질환의 사회경제적 부담.

뇌졸중 (Stroke)



[World Stroke Campaign]

치매 (Dementia)



[Alzheimer's Disease International]

정신병 (Psychiatric disorder)

[York, Canada]

신경세포를 중심으로 한 알츠하이머 치료제 연구의 실패.

홈 > 제약산업 > 제약바이오

치매 신약 후보 '솔라네주맙' 임상 실패

EXPEDITION3 연구결과…위약대비 인지기능개선 효과 미비

박미라 기

[0호] 승인 2016.11.24 15:59:39

릴리 솔라네주맙 뒤이어 머크&컴퍼니 너마저..

알쯔하이머 신약 임상 2-3상 'EPOCH 시험' 중단 발표

이덕규 기자 | abcd@yakup.com ▸기자가 쓴 다른기사 보기

기사보기 | 댓글보기 (0)

국제

머크, 알츠하이머신약 임상 중단..아밀로이드 가설 종말?

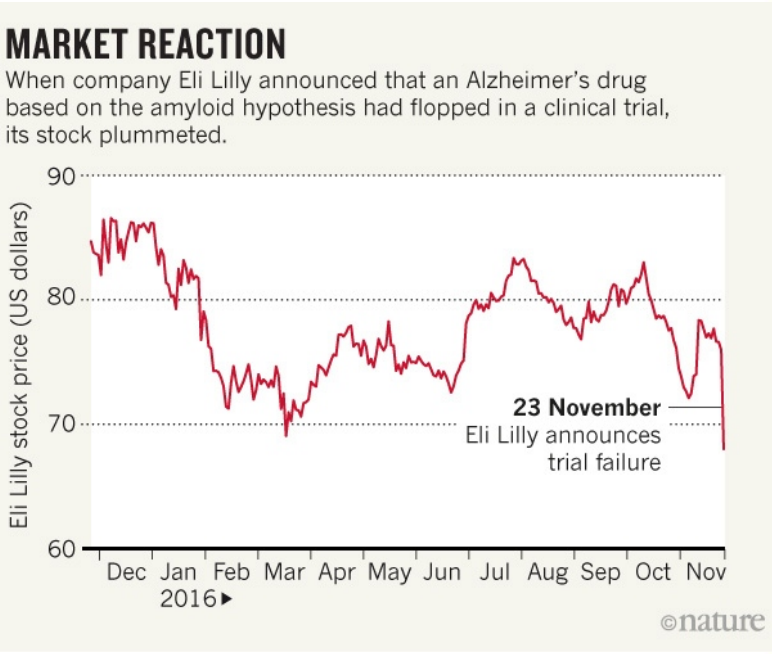
기사입력 : 2017-02-16 10:48 | 수정 : 2017-02-16 11:02

바이오스펙테이터 김성민 기자

아밀로이드 베타 겨냥하는 BACE 억제제..."성공 가능성 없어 2/3상 중단"

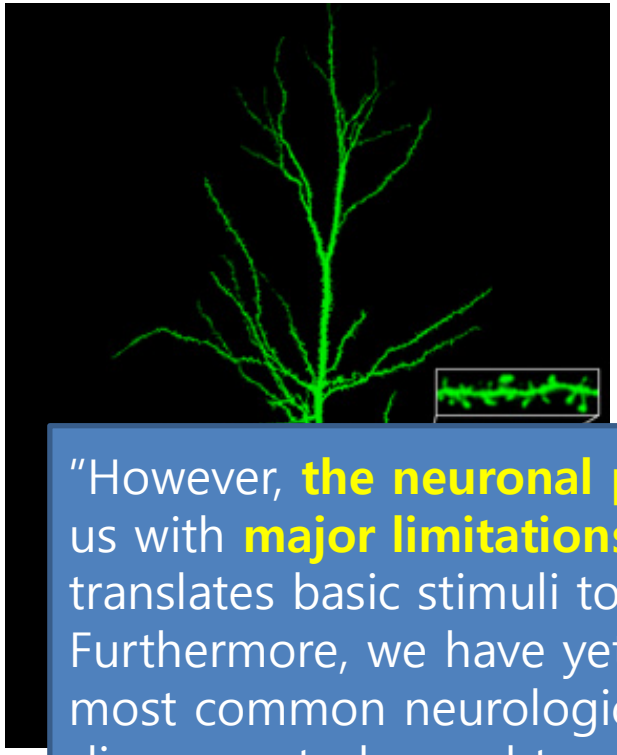
Lilly

MERCK

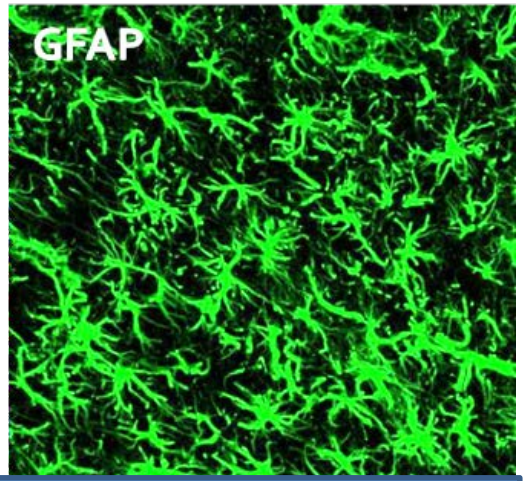


뇌연구에 패러다임 전환필요

Neurocentric

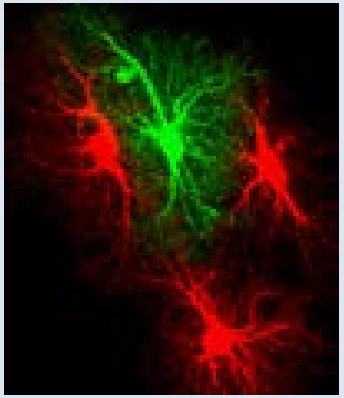


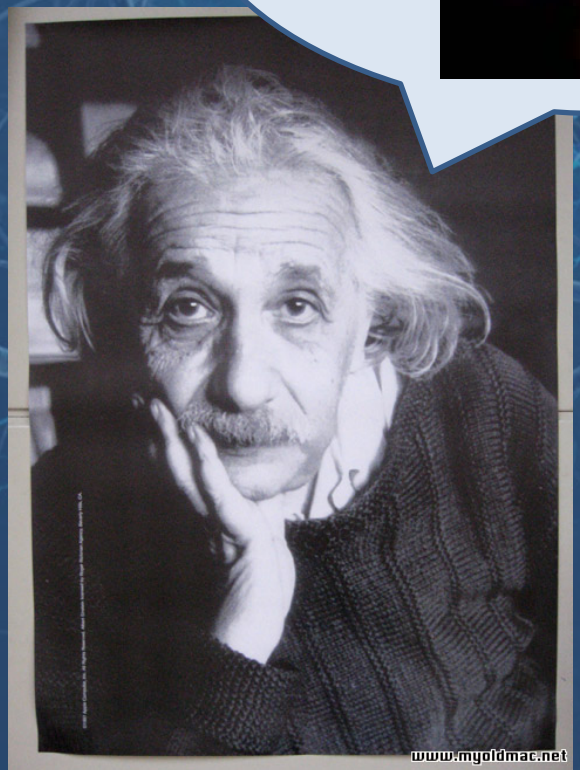
Gliocentric



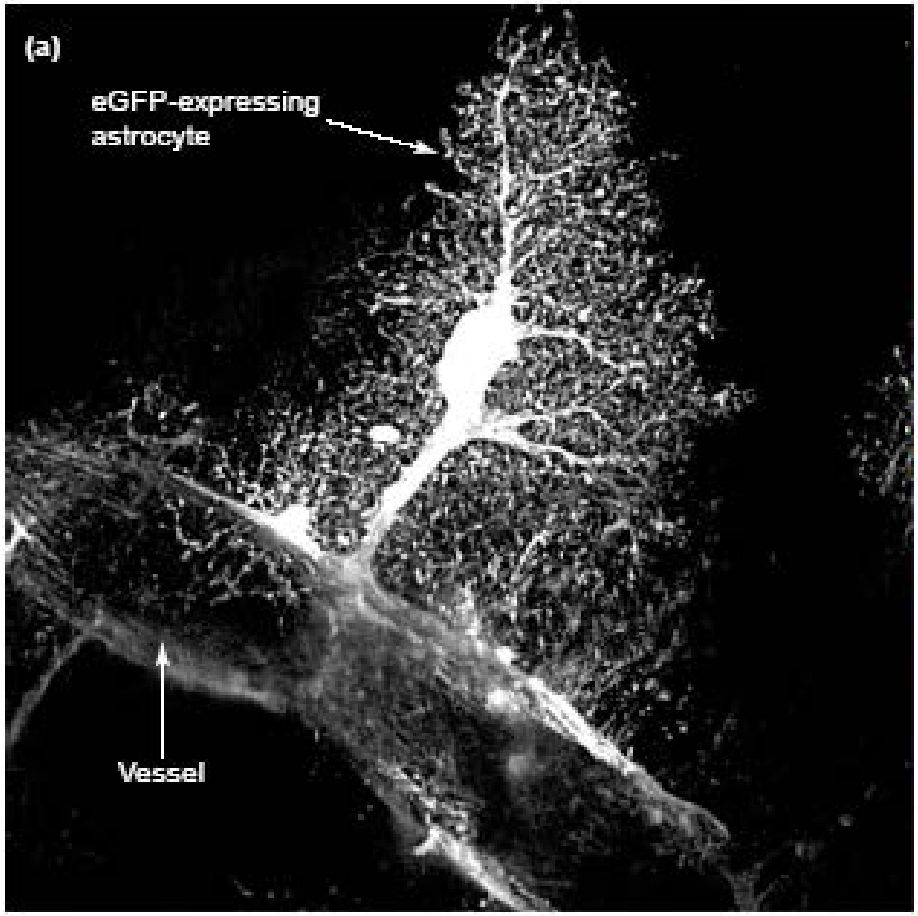
"However, **the neuronal paradigm** of studying brain function has left us with **major limitations** in our understanding of how the brain translates basic stimuli to higher order cognitive functions. Furthermore, we have yet to establish treatments for many of the most common neurological disorders, including neurodegenerative diseases, stroke, and traumatic injury of the head and spinal cord."
-**Maiken Nedergaard**

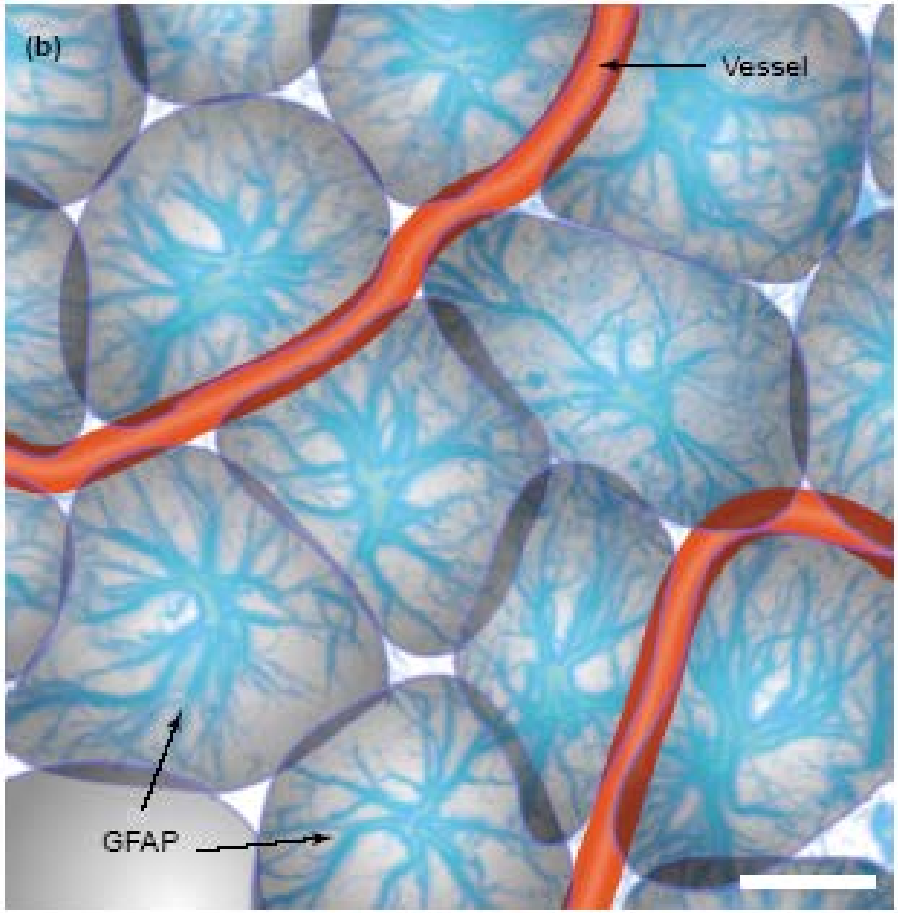
질문: Do astrocytes participate in cognitive processes?





별세포: Astrocyte 뇌세포의 60%

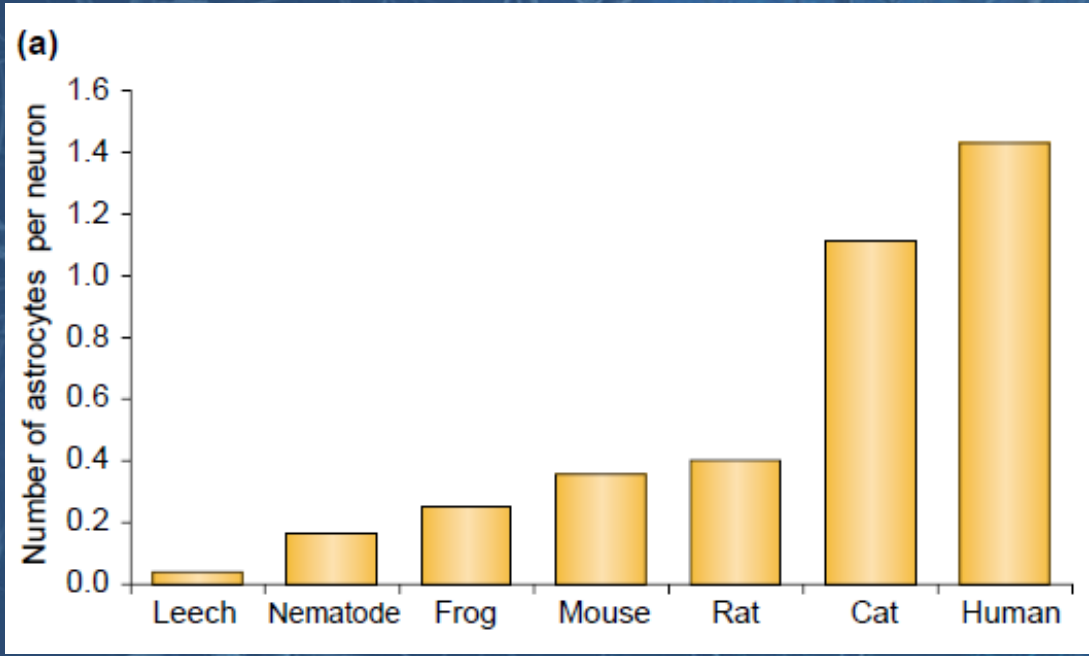


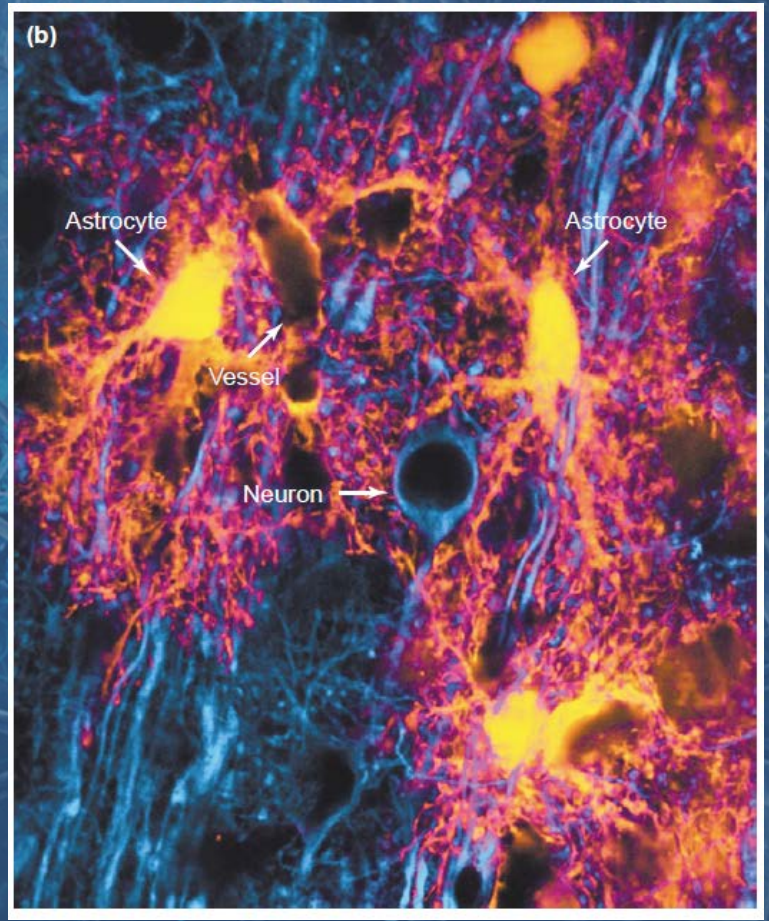


TRENDS in Neurosciences

Nedergaard M, Ransom B, Goldman SA
Trends Neurosci 2003 Oct;26(10):523-30

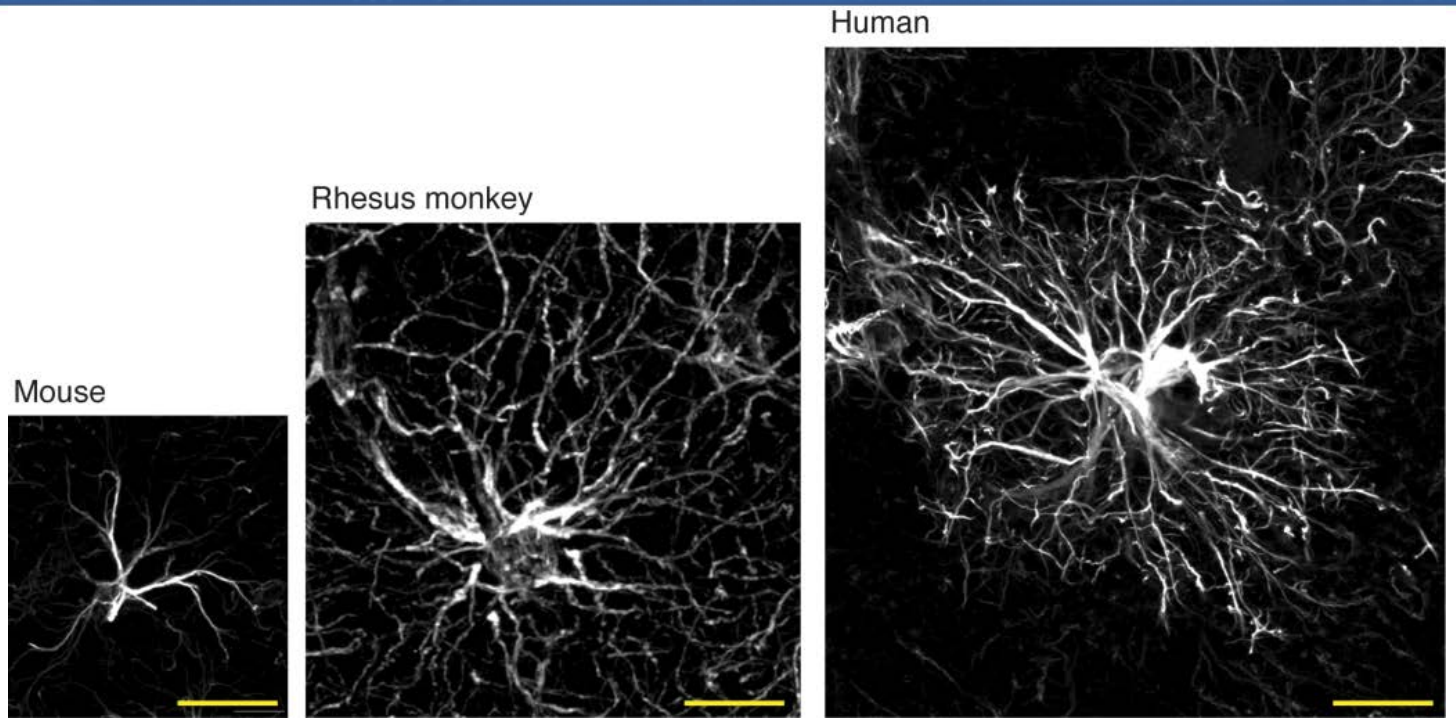
Number of Astrocyte Per Neuron

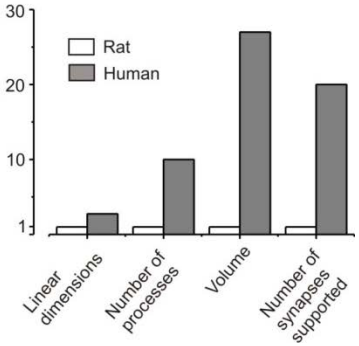




Nedergaard M, Ransom B, Goldman SA
Trends Neurosci 2003 Oct;26(10):523-30

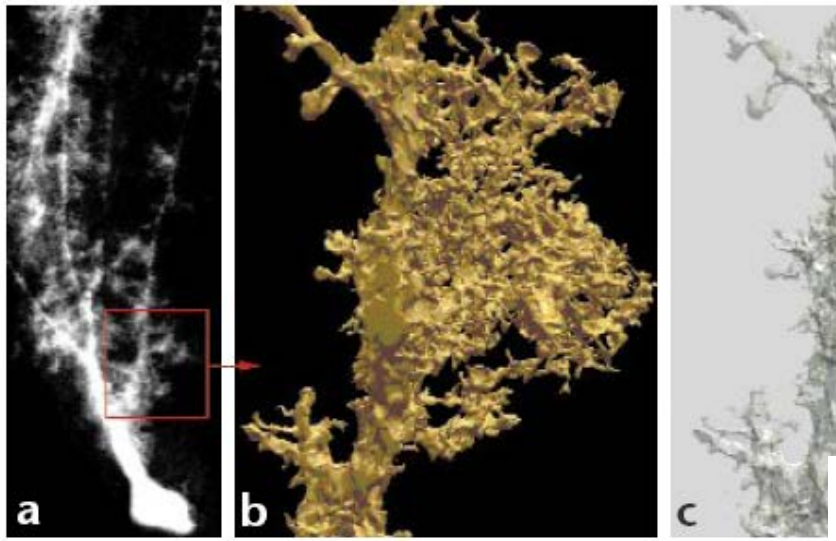
별세포 종간의 비교





Oberheim, Wang, Goldman, Nedergaard (2006): *Trends Neurosci* **29**, 547-553
Verkhratsky & Butt (2007): *Glial Neurobiology*, *A Textbook;* Wiley & Sons

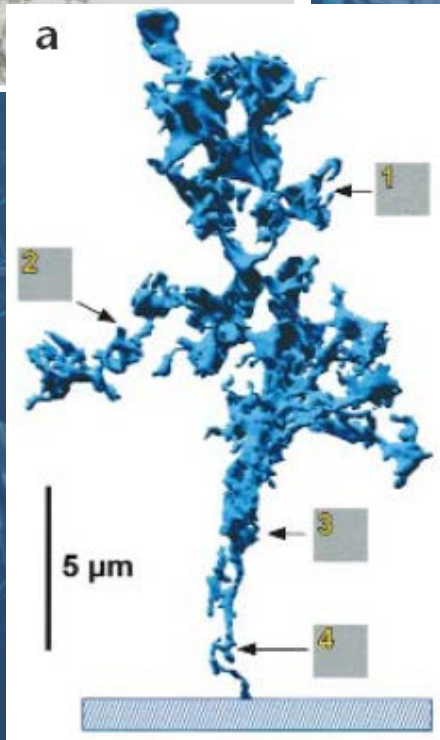
별세포의 Microdomains

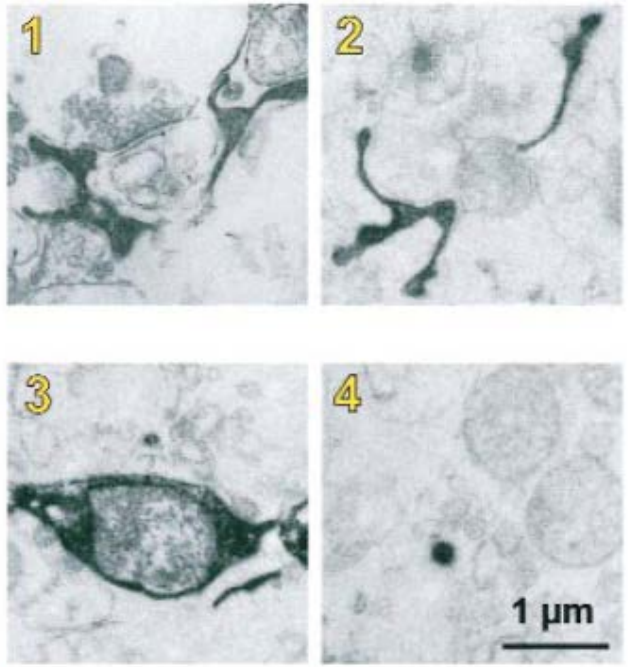


Microdomains for neuron–glia interaction: parallel fiber signaling to Bergmann glial cells

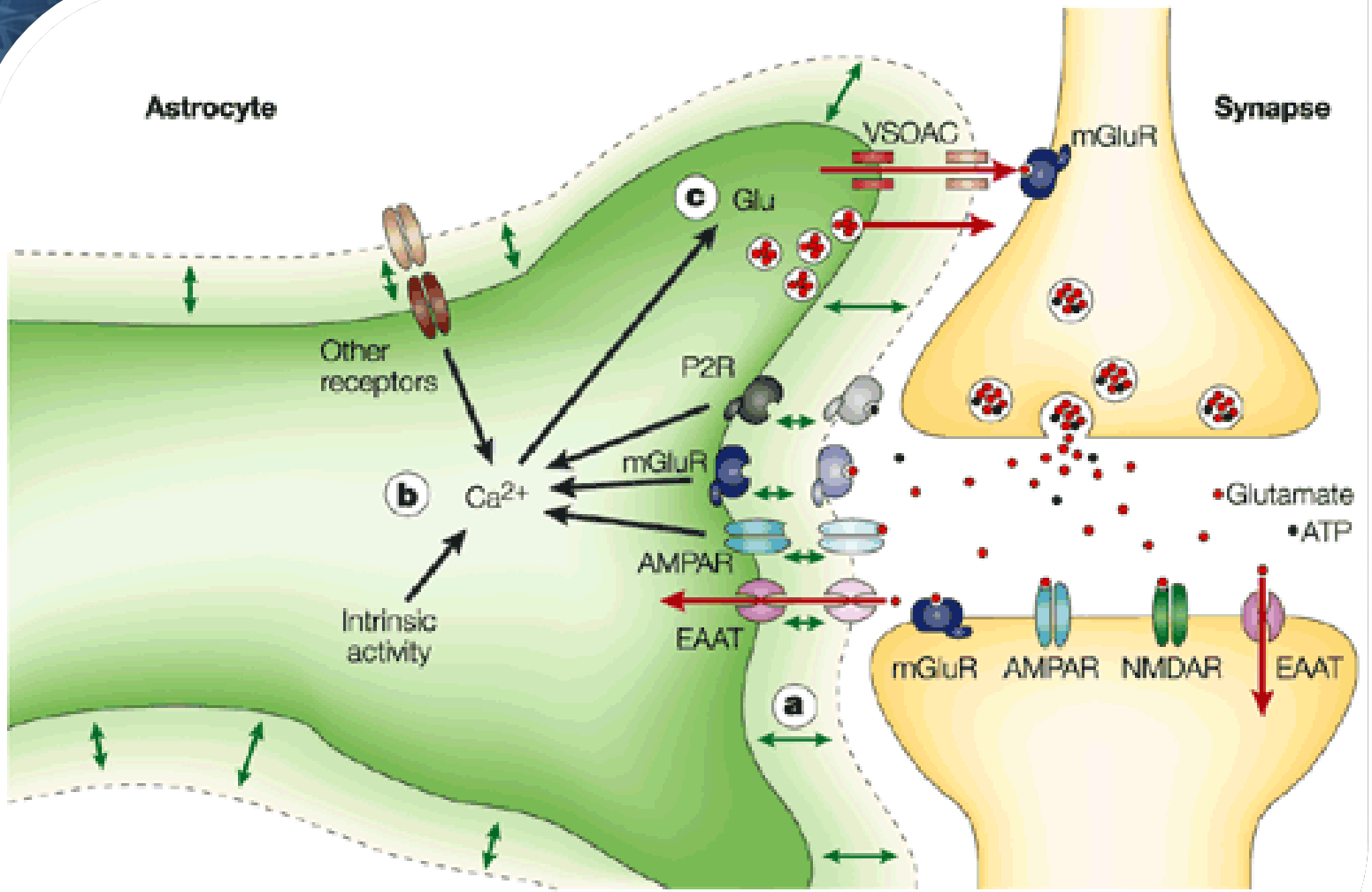
Jens Grosche[1], Vitali Matyash[2], Thomas Möller[2], Alexej Verkhratsky[2], Andreas Reichenbach[1] and Helmut Kettenmann[2]

nature *neuroscience* • volume 2 no 2 • february 1999



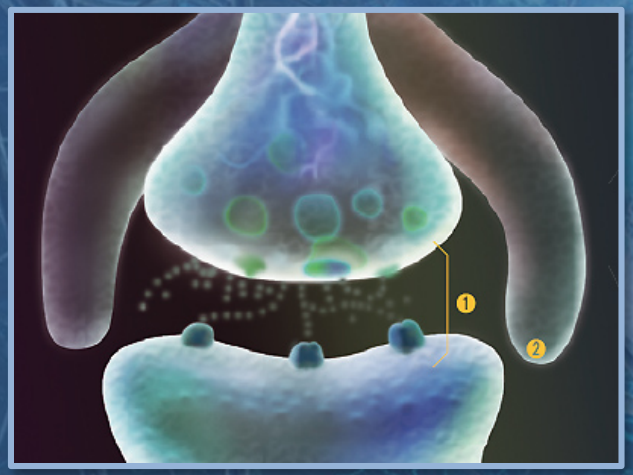


시냅스와 밀접한 관계

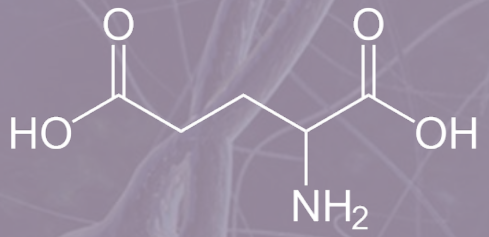

Astrocyte
Synapse
VSOAC
mGluR
c
Glu
Other receptors
P2R
mGluR
b
Ca2+
Glutamate
ATP
AMPAR
Intrinsic activity
EAAT
mGluR
AMPAR
NMDAR
EAAT
a
Nature Reviews | Neurosci

시냅스 신호전달

Synapse



Excitatory transmitter : Glutamate

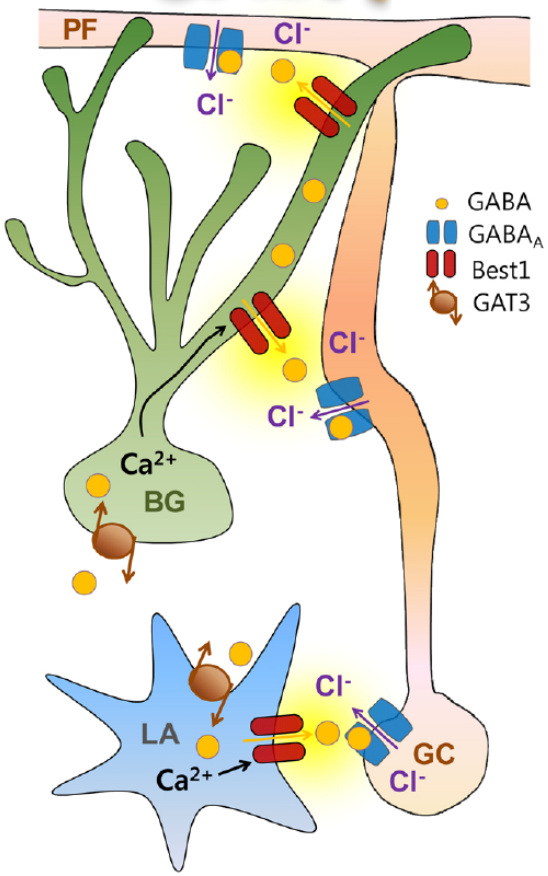


Inhibitory transmitter : GABA

So far, only neurons are known to produce and release Glutamate and GABA.

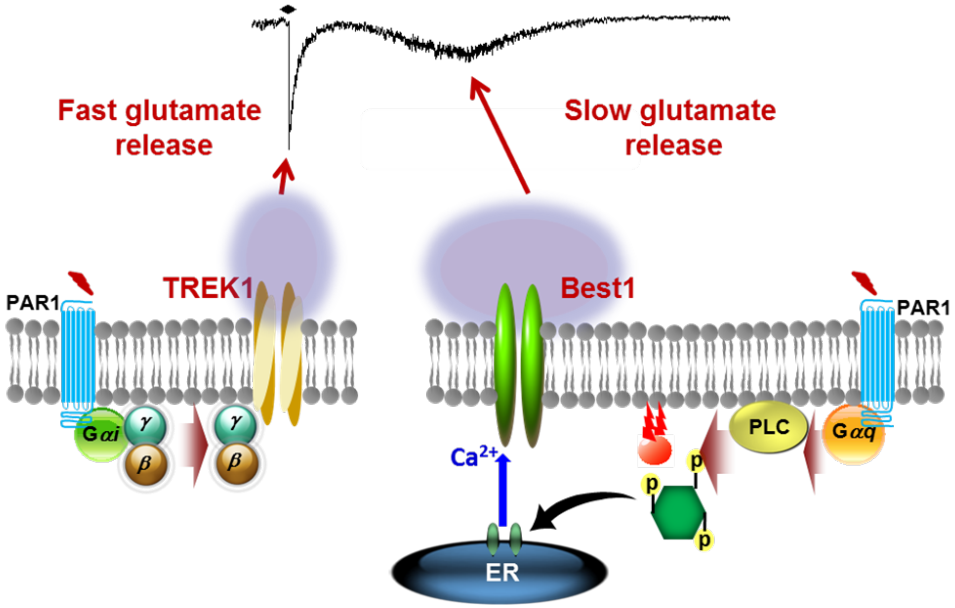
별세포에서의 채널을 통한 GABA/glutamate 분비

GABA



Science, 2010 (교신저자)

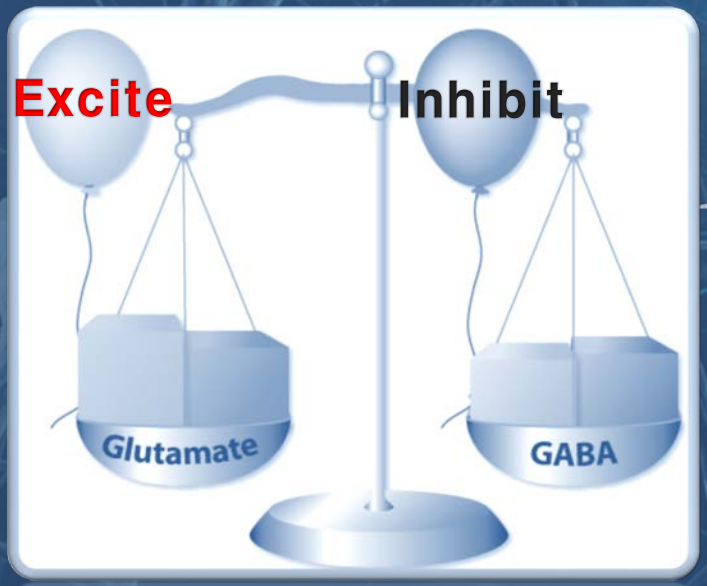
Glutamate



Cell, 2012 (교신저자)

Glutamate/GABA 밸런스에 기여

Imbalance of Glutamate/GABA causes various neurological disorders.



Insomnia

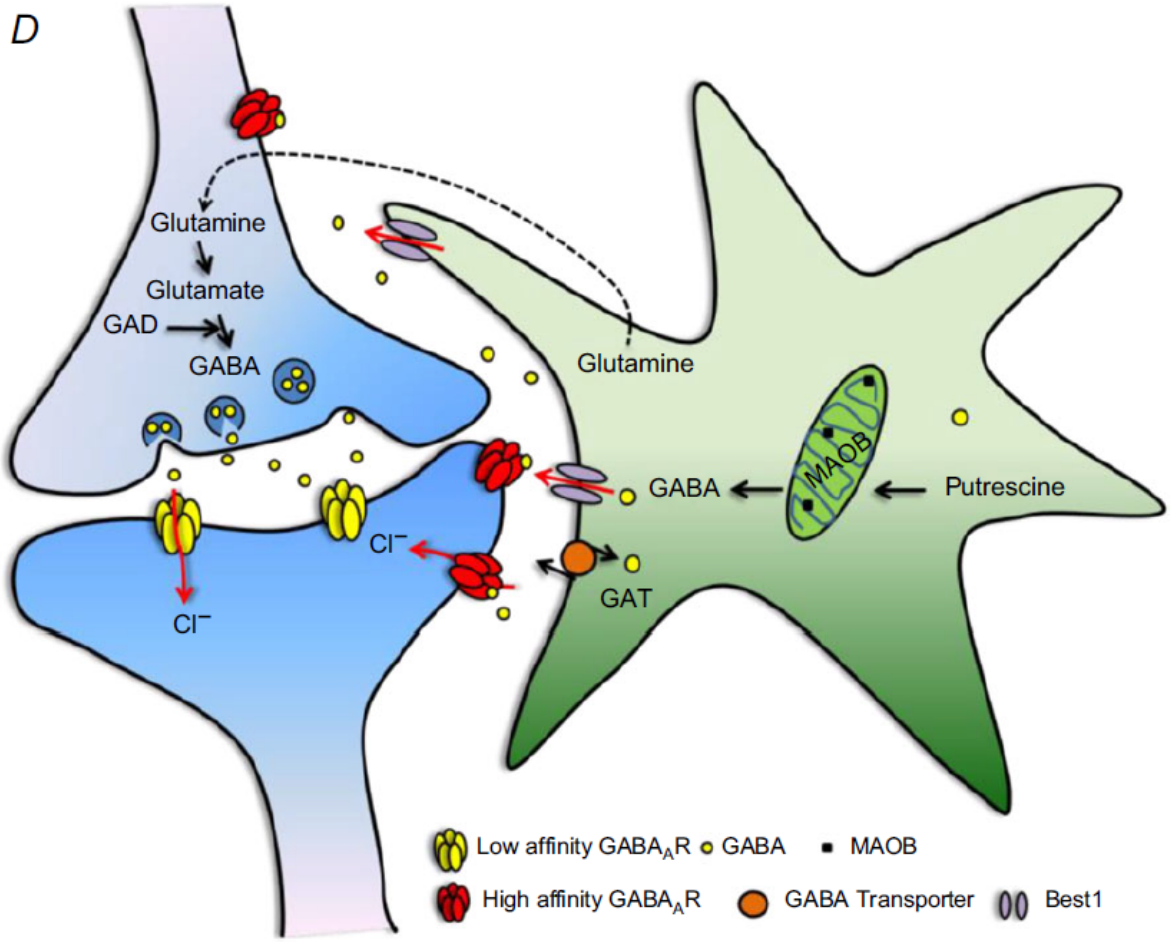
Depression

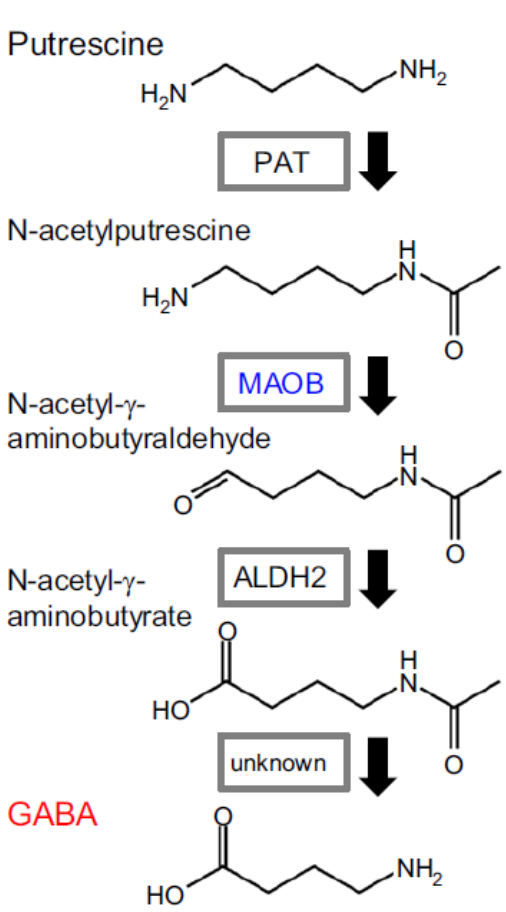
Epilepsy

Motor Impairment (PD)

Learning & Memory Impairment (AD)

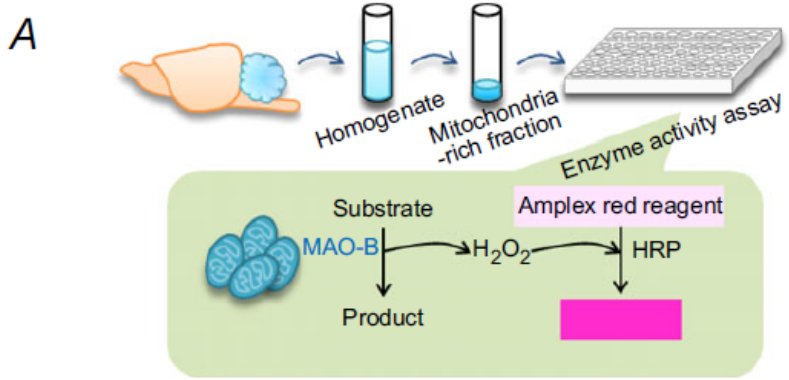
별세포의 GABA: MAOB (monoamine oxidase B)에 의해 생성

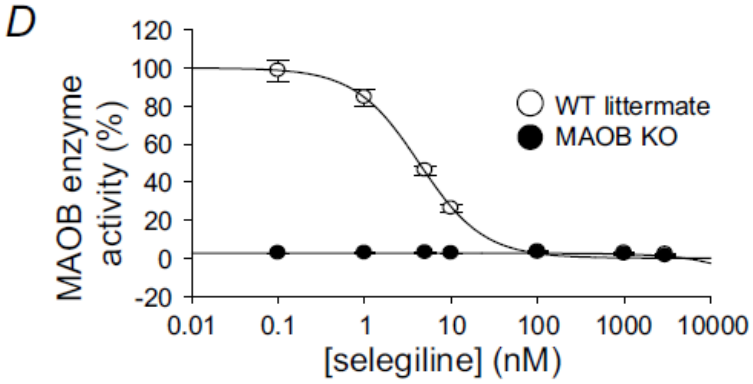


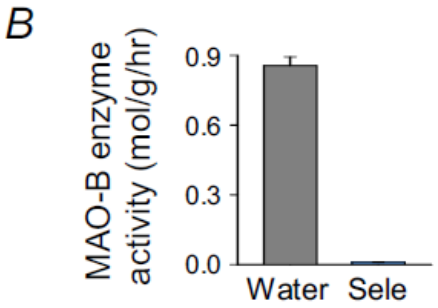


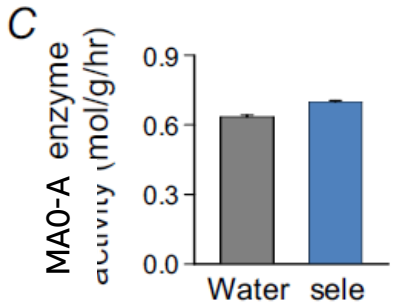
Yoon et al., 2014 J Physiol

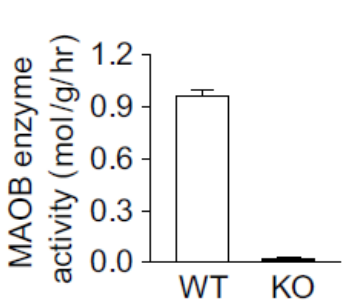
별세포의 GABA: MAOB (monoamine oxidase B)에 의해 생성

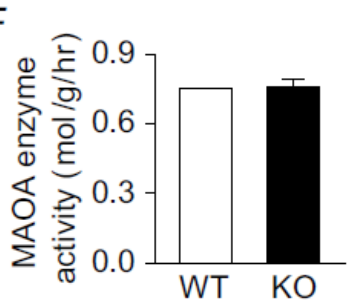


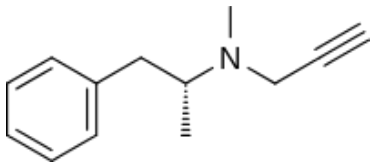










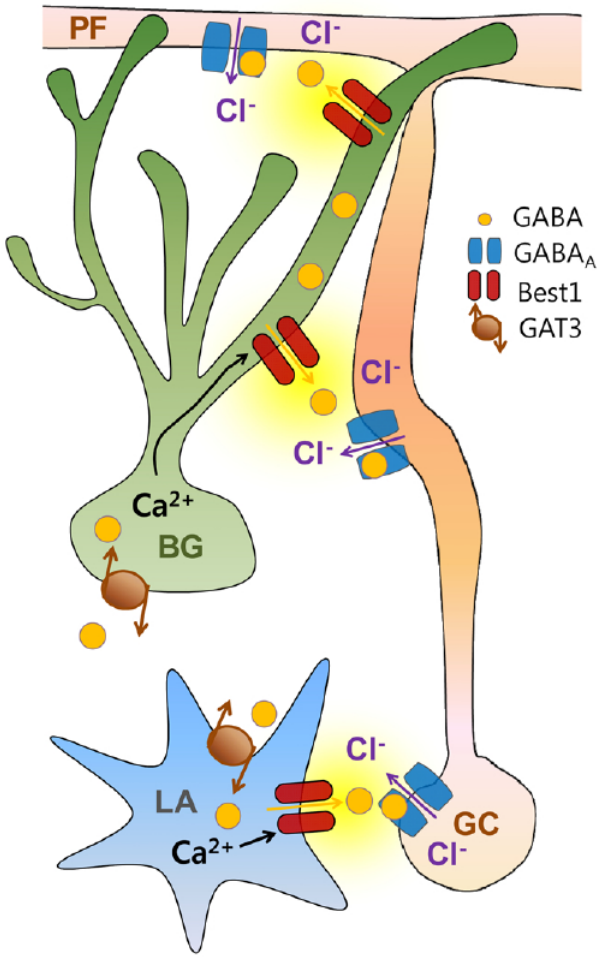


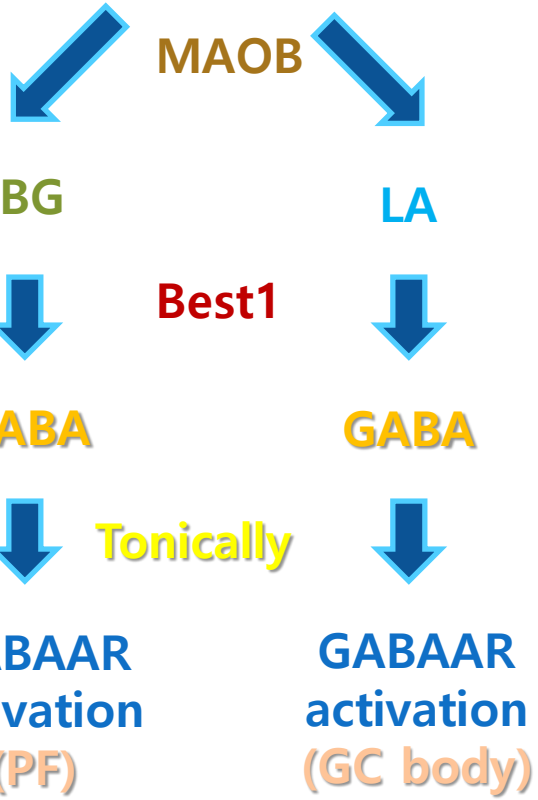
Selegiline (irreversible)

현재 파킨슨씨병 치료제로 사용

Yoon et al., 2014 J Physiol

The model of tonic GABA release in cerebellum



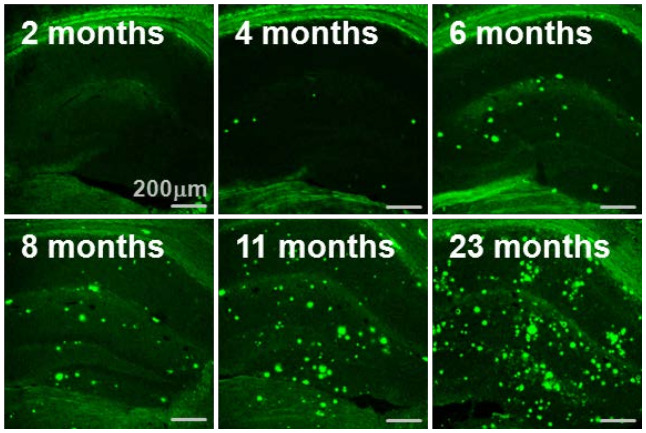


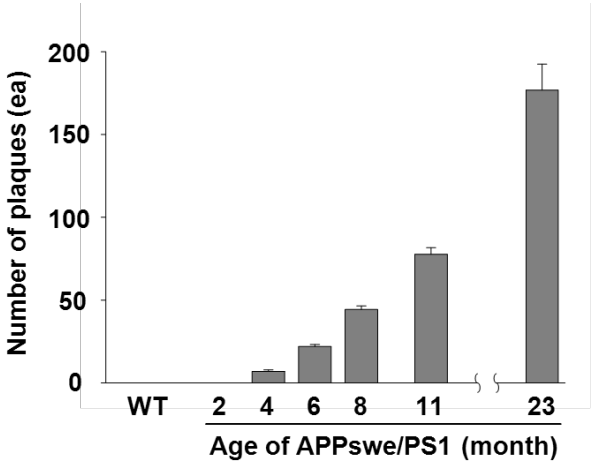
Bo-Eun Yoon

Lee & Yoon et al., 2010 *Science*; Yoon et al., 2011 *Mol Brain*; Yoon et al., 2014 *J Physiol*

Tonic GABA release from reactive astrocytes in Alzheimer's Disease

APP/PS1 double transgenic mice



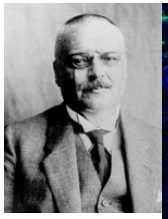


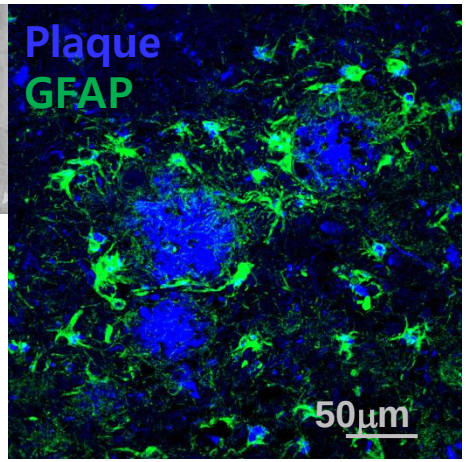
Seonmi Jo

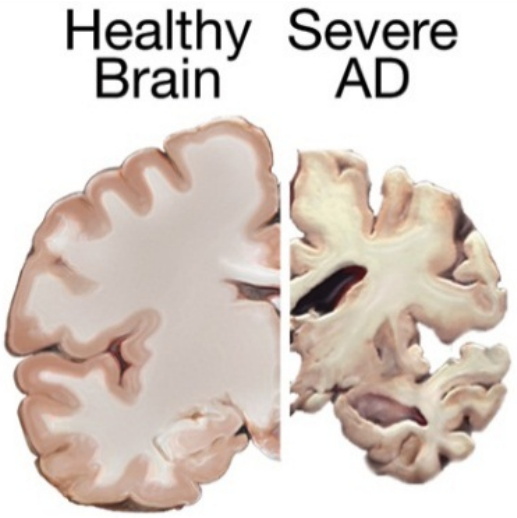
GiD: Inducible Diphtheria toxin receptor(iDTR) controlled by GFAP promoter

Dr. Daesoo Kim

반응성 별세포







Healthy

Reactive astrocytosis

GFAP ↑, Vimentin ↑

Ca^{2+}

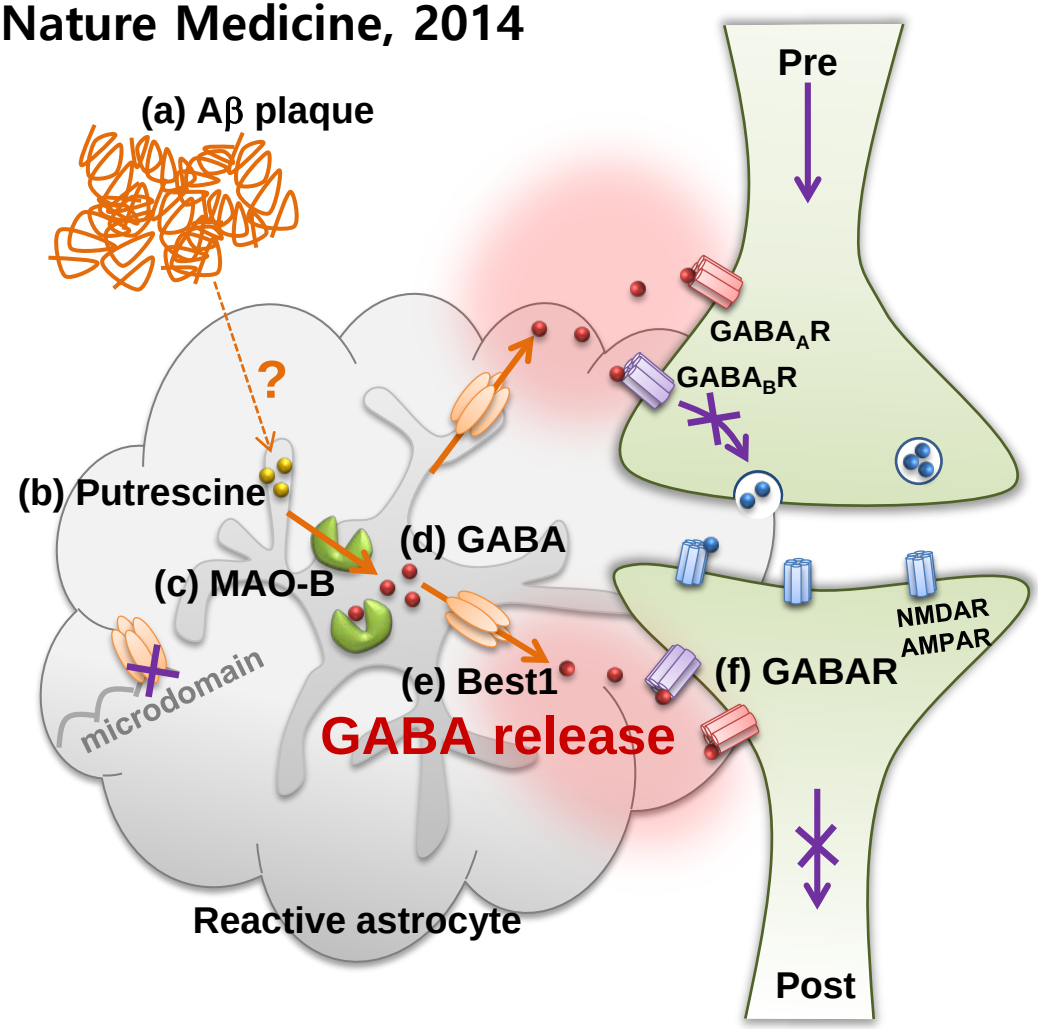
Hypertrophy
Molecular & Functional Changes

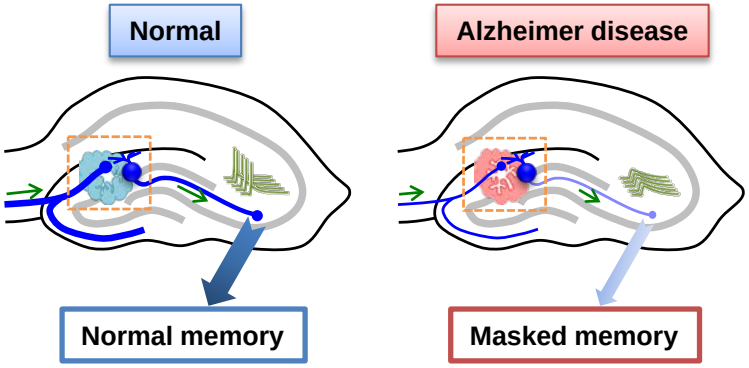
Hypertrophy
Molecular & Functional Changes
Proliferation

Scar formation

알츠하이머성 치매 기억상실 원인 규명

Nature Medicine, 2014





GABA from reactive astrocytes

↓

Inhibition on granule cells (PP-DG synapse)

↓

Impairment in synaptic plasticity

↓

Memory impairment

Novel roles of astrocyte in Alzheimer disease

- GABA production (by MAO-B) and release (through Best1)
- GABAergic inhibition on neuron to mask memory

KDS2010 as an effective AD drug to replace selegiline

Excellent solubility ..... Water soluble, >50mg/mL

Low CYP inhibition ..... 2C19, 2D6, 2C9, 1A2, 3A4 IC_{50} > 10 μM

Binding assay: IC_{50} > 50μM

Low hERG inhibition

Brain-to-plasma ratio (B/P) at 2 hr (oral) > 10

Excellent BBB penetration

Microsomal stability (human) 92 % remaining after 30 min

Plasma stability (human) 98 % remaining after 30 min

Excellent stability

Plasma	Intravenous	Oral
$AUC_{0-\infty}$ (μg min/ml)	202.8 ± 25.47	259.34 ± 18.76
C_{max}(μg/ml)		0.84 ± 0.13
T_{max} (min)		113
F (%)	~ 100%	

Excellent PK

Excellent Druglike Properties

KIST 치매치료후보물질 메가바이오숲에 60억 받고 기술이전

국가과학기술연구회 융합연구사업 첫 대형성과

박희범 과학기술전문기자 승인 2017.05.31 19:04

(주)케미메디 최건섭 대표이사, (주)케미메디 황성연 회장, (주)메가바이오숲 박상민 대표이사, KIST이병권 원장, 국가과학기술연구원(NST) 이상천 이사장(왼쪽부터)이 31일 치매치료 후보물질 기술이전 조인식을 가진뒤 기념촬영했다.

한국과학기술연구원(KIST, 원장 이병권)과 ㈜케미메디(대표이사 최건섭)의 계열사인 ㈜메가바이오숲(대표이사 박상민)은 31일 KIST 서울 본원에서 '알츠하이머성 치매 치료 후보약물'에 대한 기술이전 조인식을 가졌다.

기술이전 총 계약금은 60억 원이다. 선급금 5억 원(현금)과 진행에 따른 마일스톤 기술료 55억 원이 포함되어 있다. 경상기술료는 순 매출액의 3%이다.

오늘의 주요뉴스


[정책]
주목받는 과학기술혁신본부....수장 누가오나?


[과학기술]
KIST-벨라루스 국립과학원(NASB) MOU


[과학기술]
KIOST, 차세대 복합위성 활용 공동 워크숍 열어


[Biz+]
세종시 사업자 1년만에 31% 증가한 6962개소

반응성별세포의 GABA: 다양한 퇴행성 뇌질환에 적용.

공통 핵심 기전

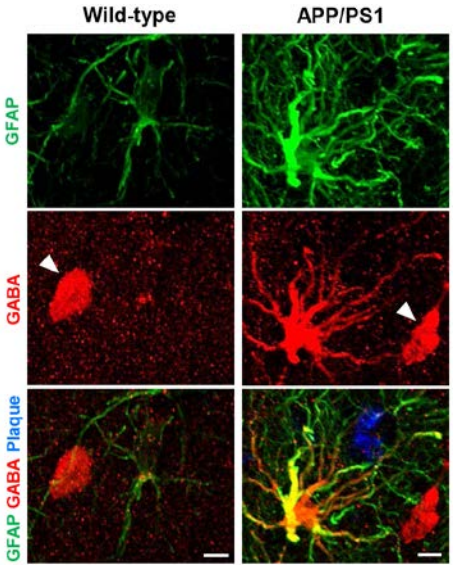
반응성 교세포

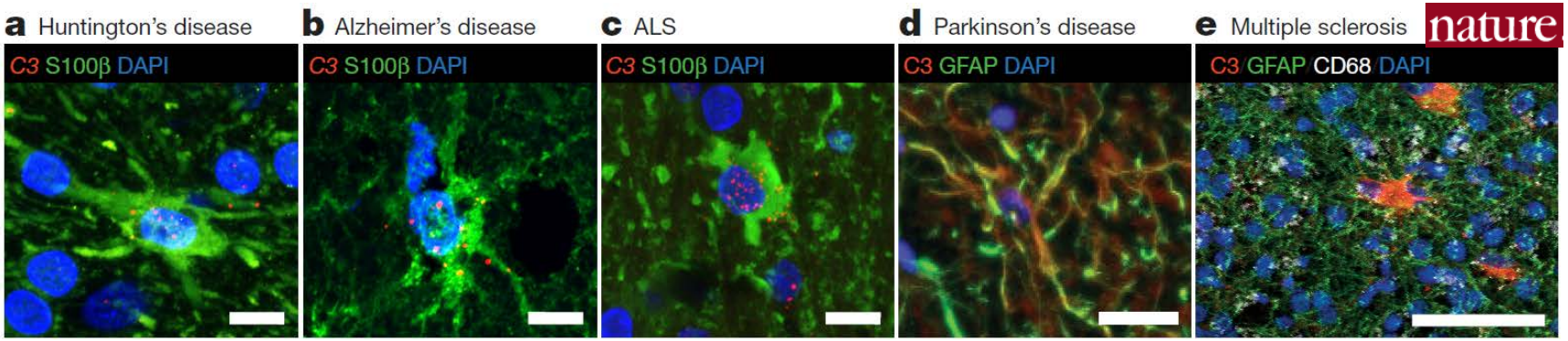
치료 핵심 타겟

비가역적

신경세포 손상

- 알츠하이머병
- 파킨슨병
- 헌팅턴병
- 루게릭병
- 뇌졸중
- 뇌종양
- 척수손상





Center for Cognition and Sociality at IBS