

치매 신약개발 어디까지 왔나?

- Jong Sung Koh, Ph.D. (사대 75')
- President & CEO, GENOSCO
- March 6, 2022



서울대학교 뉴잉글랜드 동창회 주최
온라인 뉴잉글랜드 포럼

고종성 박사
CEO, GENOSCO

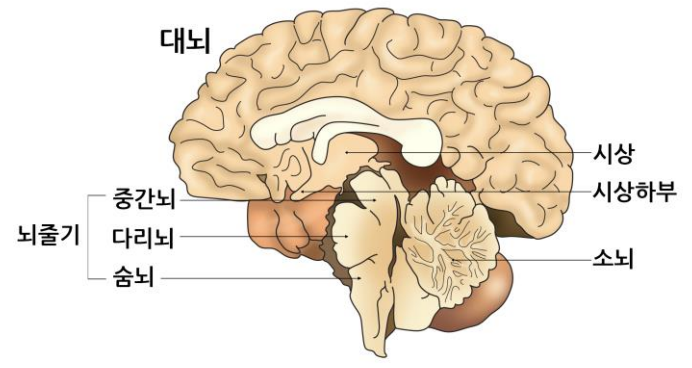


치매(알츠하이머) 신약개발
어디까지 왔나?

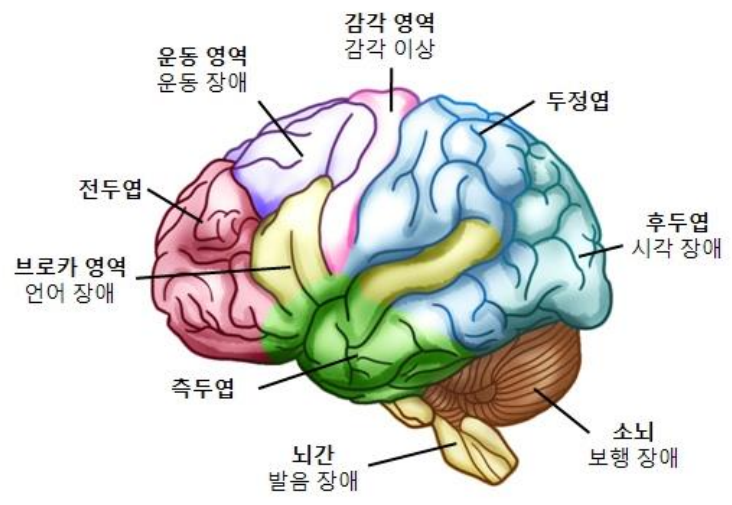
3월 6일 (일)
저녁 7시반

www.snuaane.org
snuaane@gmail.com

뇌?-머리뼈로 잘 보호됨



【 대뇌 】

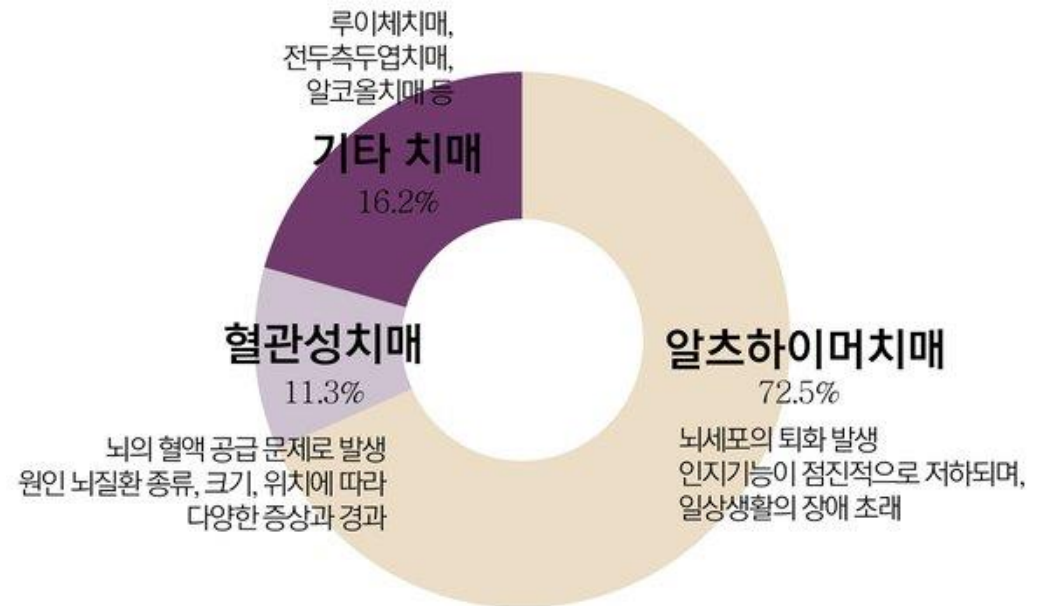


치매(Dementia)란?

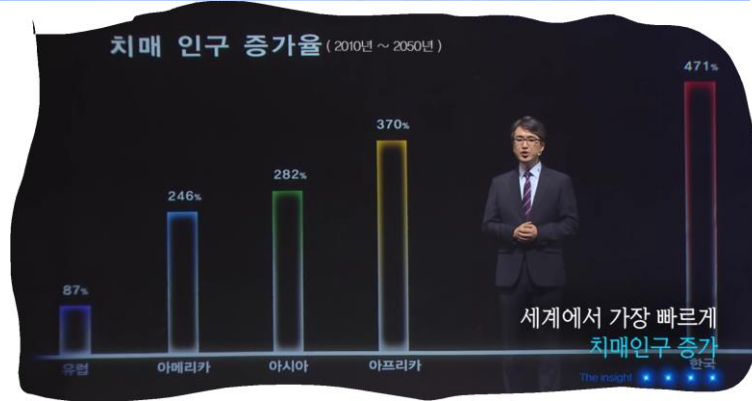
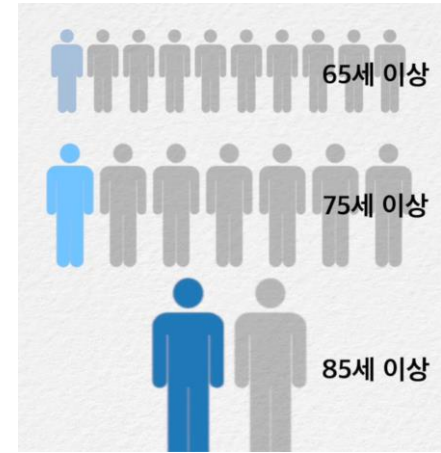
“치매란 정상적으로 성숙한 뇌가 후천적 외상이나 질병등 외인에 의하여 손상 또는 파괴되어 전반적으로 인지능력, 행동, 기능적 상태 및 정신기능이 떨어지는 복합적인 증상”

치매의 종류

1. 알츠하이머: 가장 흔한 치매
2. 혈관성 치매: 뇌졸중등에 의한 치매
3. 루이소체/파킨스병 치매: 비정상 신경섬유 축적
4. 기타: 전두측두엽 치매등



치매 환자수



세계적으로 4초에 한명, 하루 약 21,600명 발생
2050년 1억명 예상

한국은 가장빠르게 증가로 2050 치매환자 300만시대
비용 현재 17조에서 2020년에 100조 예상

각 치매 병태생리



베타아밀로이드 가설
타우단백질 가설
아세틸콜린 가설
신경염증 가설
Apo E4가설



뇌졸중
심혈관계 질환
-고혈압/콜레스테롤
-당뇨
-흡연



alpha-synuclein 가설
아세틸콜린가설

알츠하이머의 진행



정상



치매 초기

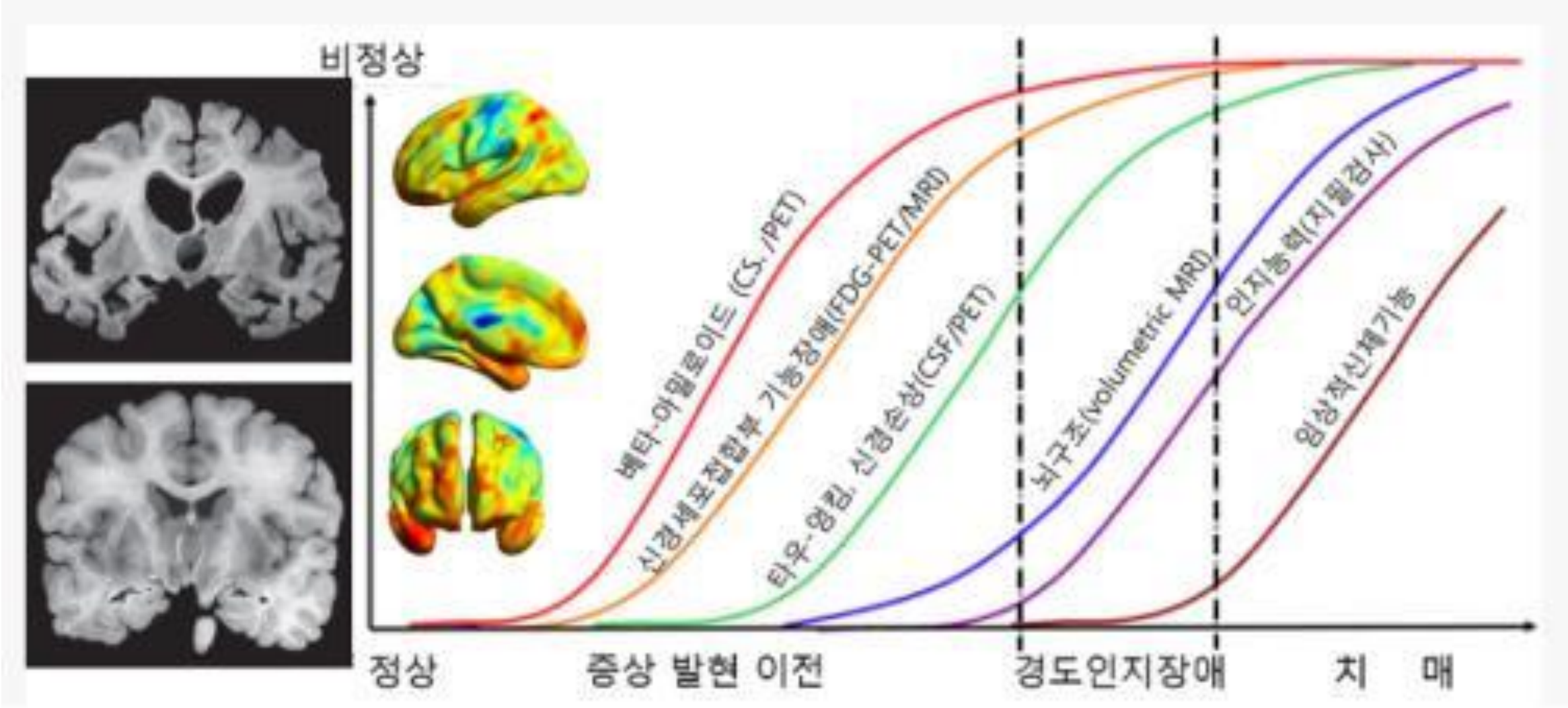


중기



말기

알츠하이머 진행: 바이오마커와 영상기술



알츠하이머 환자 뇌

일반인의 뇌

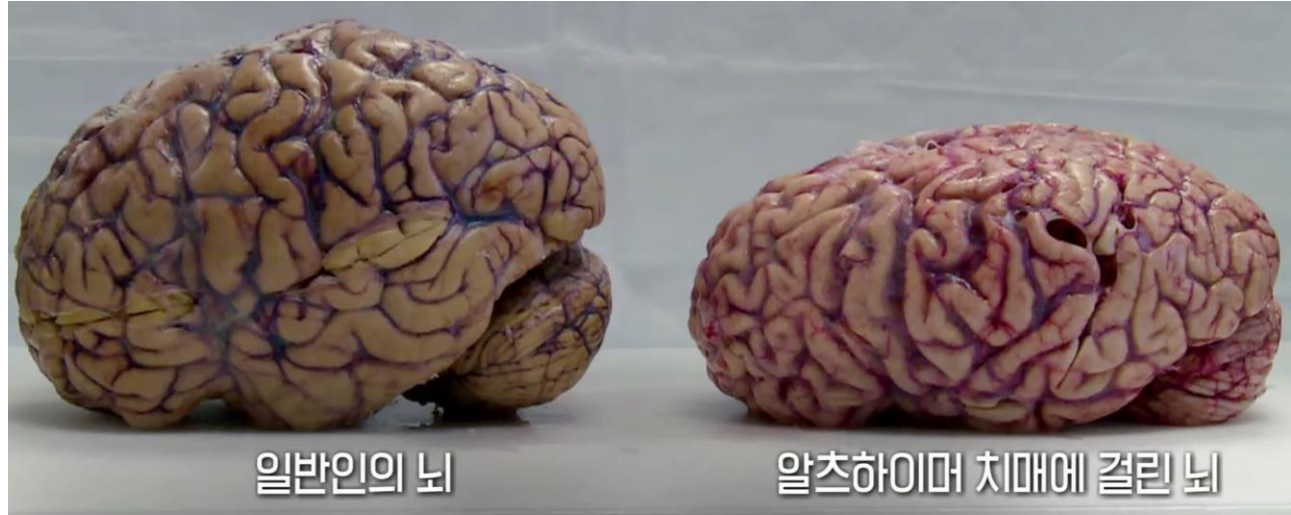
남자: 1,400그램

여자: 1,250그램

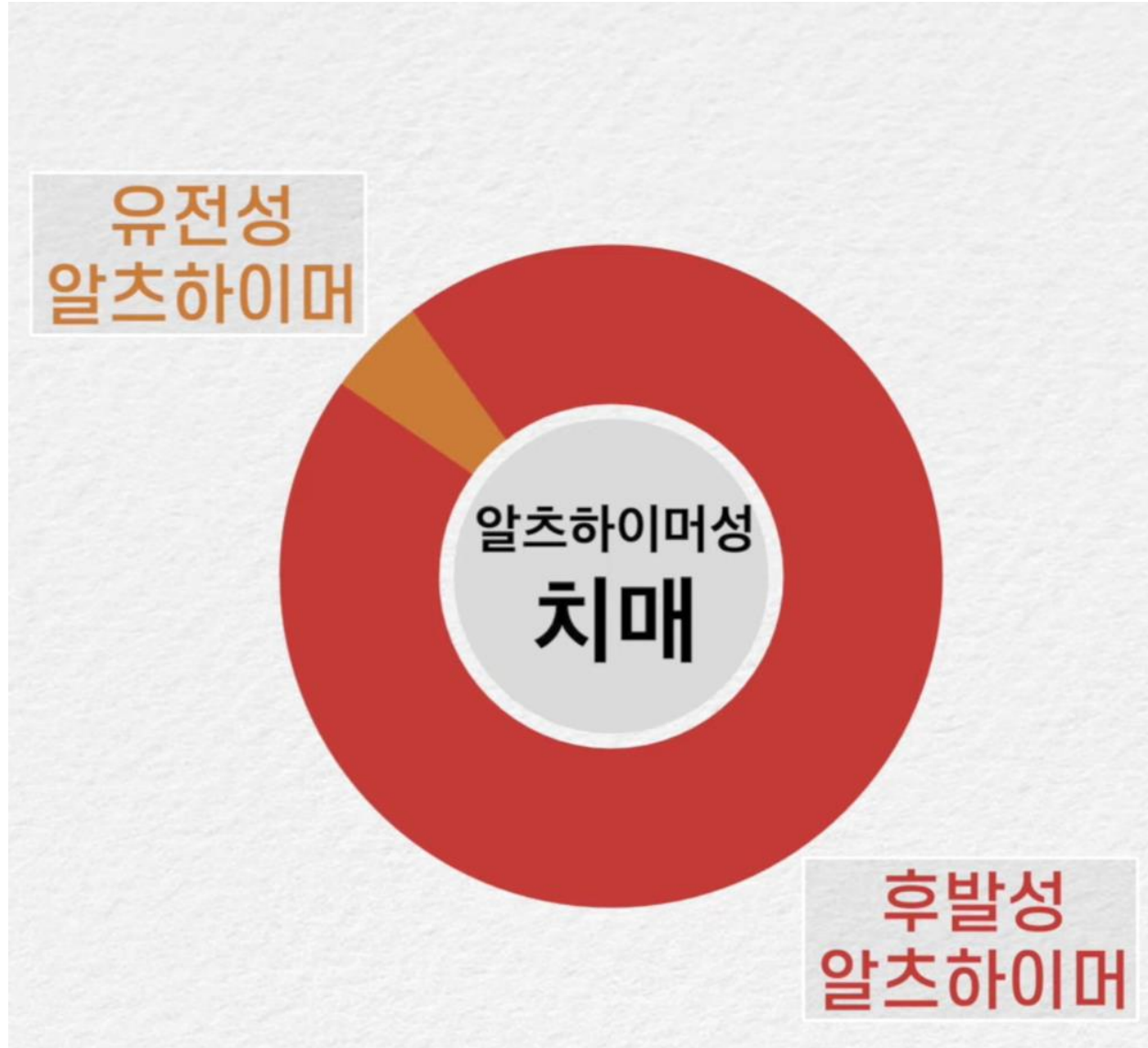
1000억개의 신경세포

하루 2-10만개의 뇌세포 줄어들음

알츠하이머: 여성 > 남성

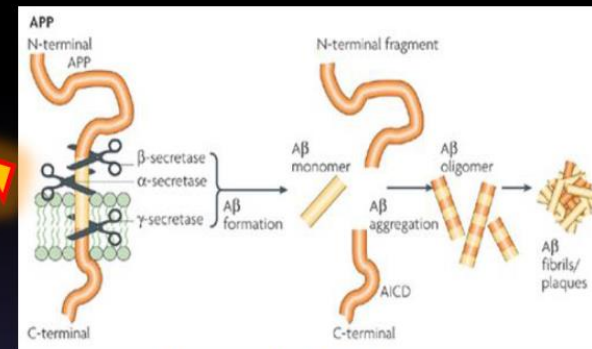
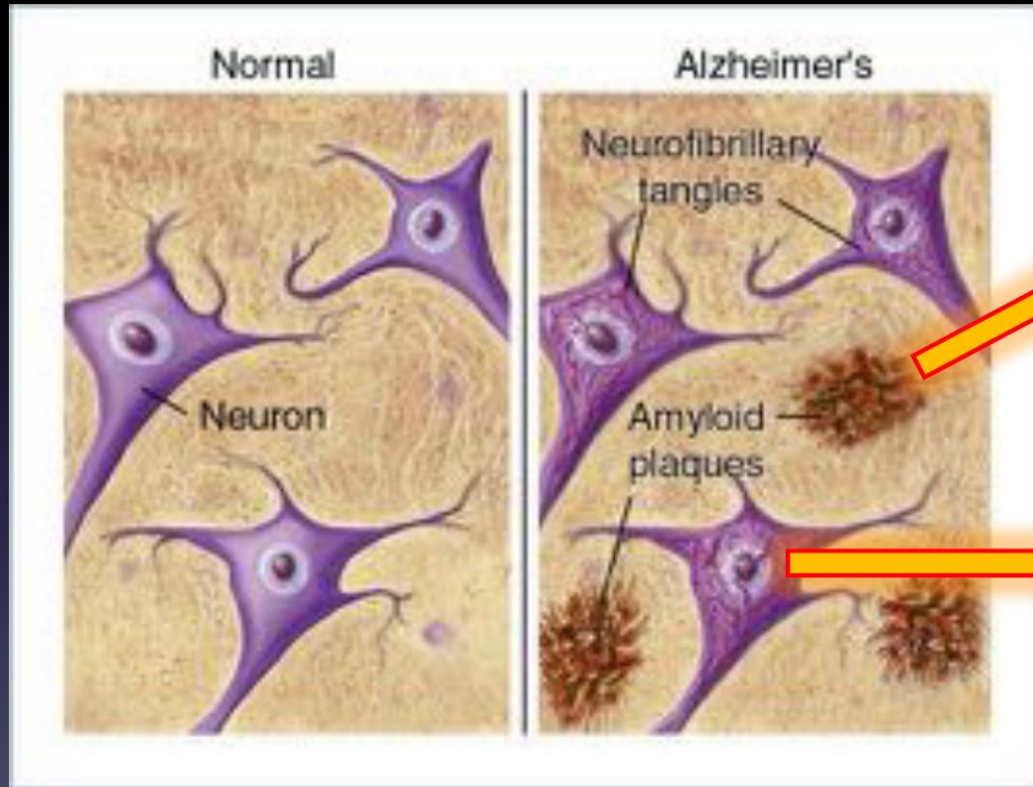


알츠하이머 종류

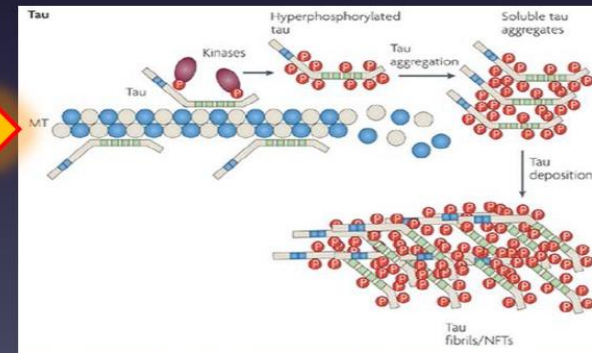


알츠하이머 병인 이론

β -amyloid plaques and neurofibrillary tangles: hallmarks of Alzheimer's disease



β -amyloid plaques



Neurofibrillary tangles (NFT)

$A\beta_{42}/A\beta_{40}$:
AD Biomarker

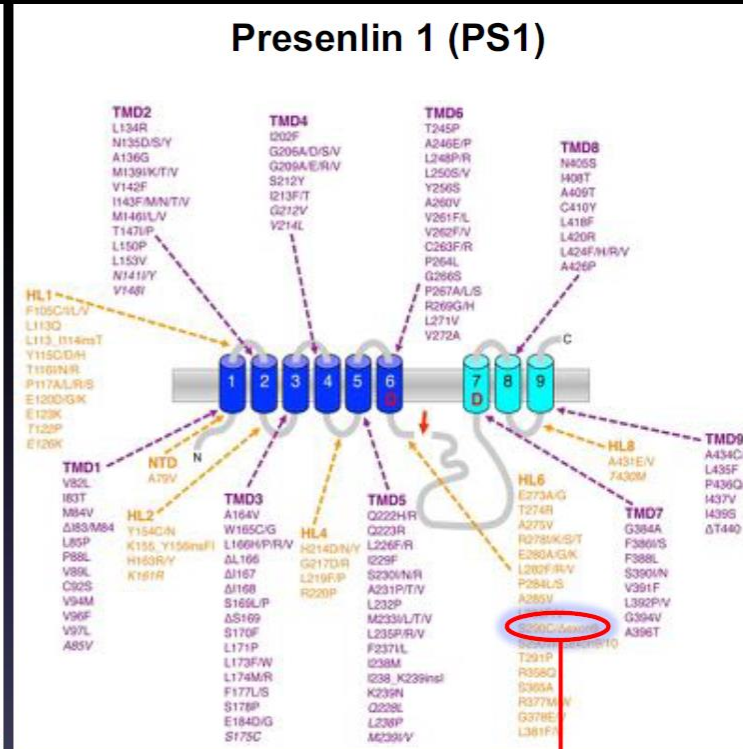
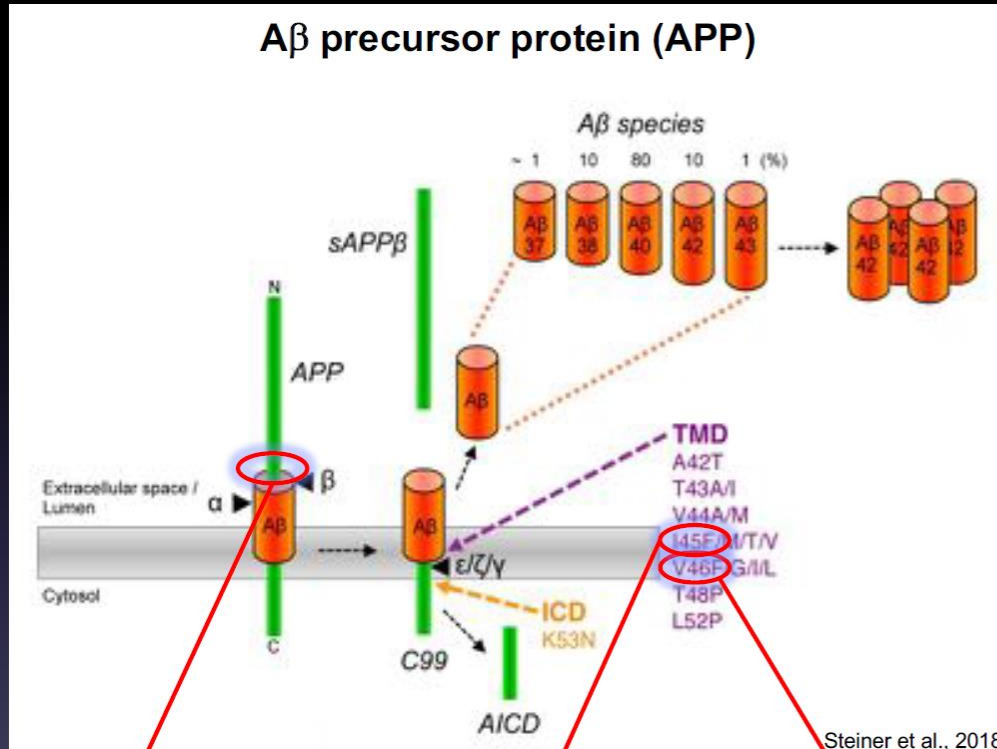
*Doo Yeon Kim/Nature
Communication, 2020*

P-tau-181:
AD Biomarker
*Nature Medicine,
2020*

Gotz J, and Ittner LM, Nature Reviews Neuroscience 9, 532-544

유전성 알츠하이머

Introducing multiple familial AD mutations to increase pathogenic A β levels



Swedish,
total A β $\uparrow\uparrow$

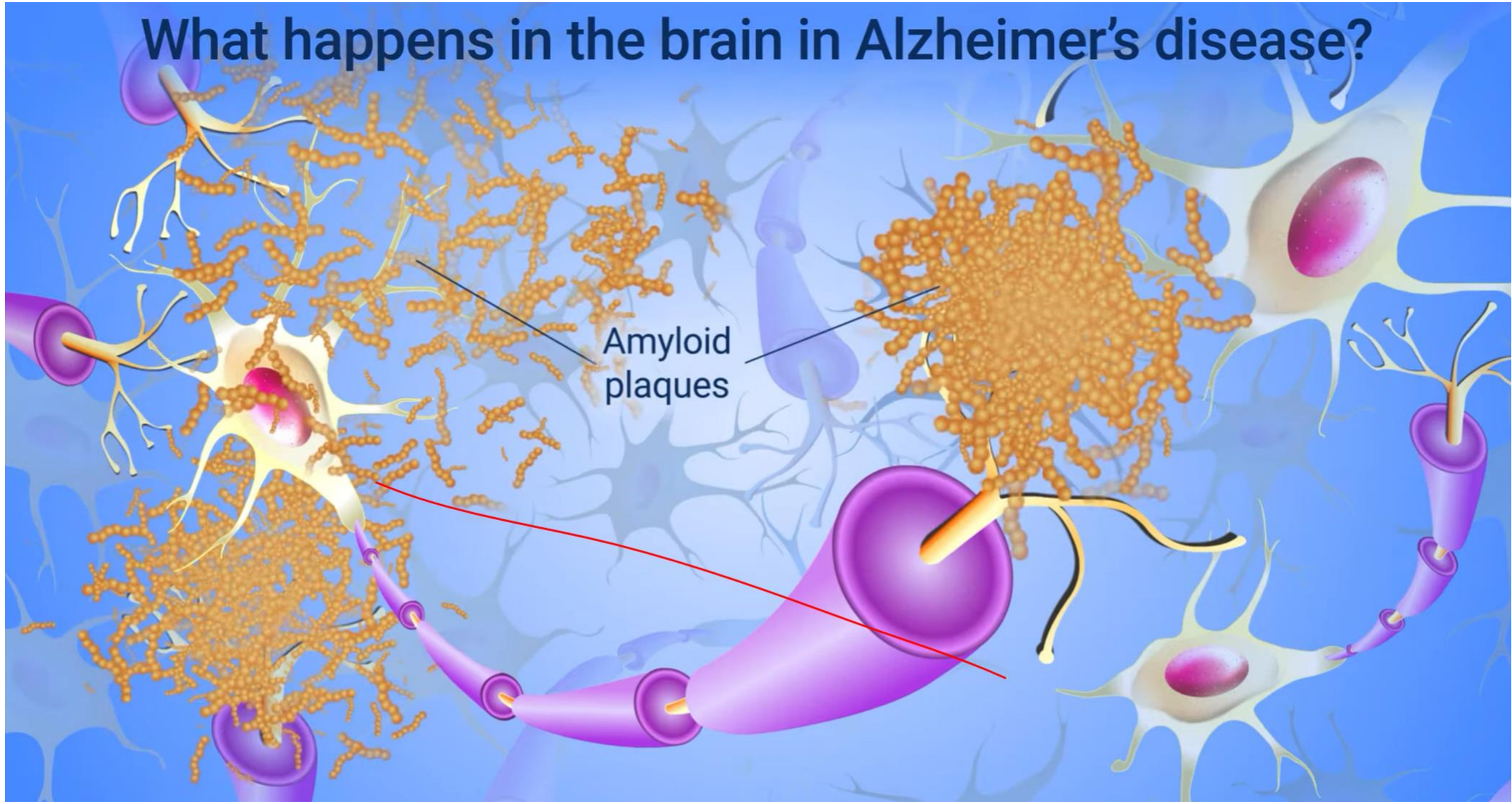
Iberian,
A β 42/40 ratio $\uparrow\uparrow$

London,
A β 42/40 ratio \uparrow

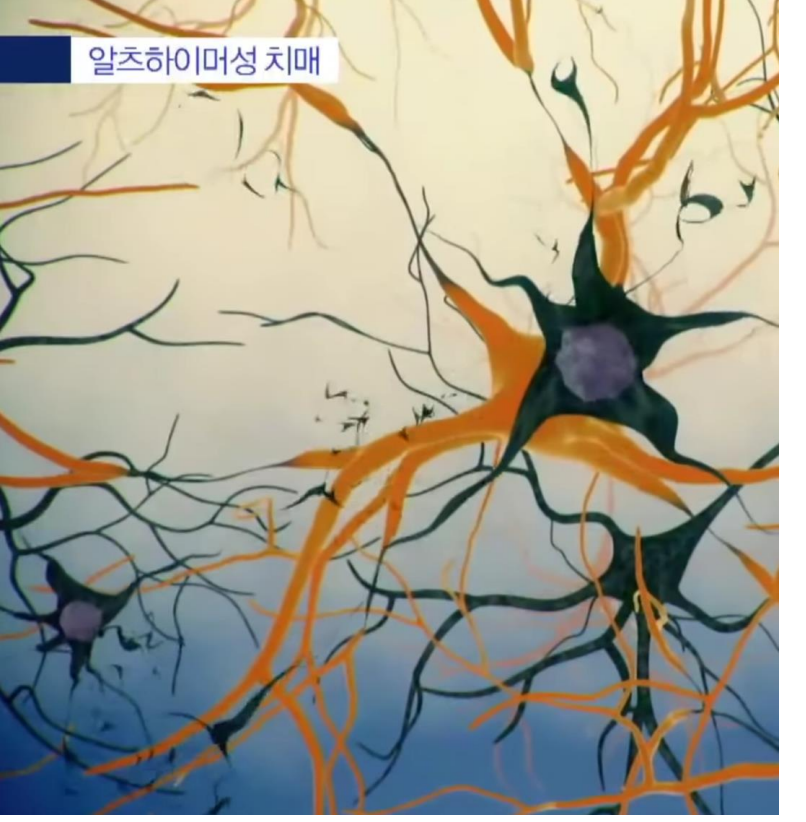
PS1 Δ E9,
A β 42/40 ratio $\uparrow\uparrow$

Beta-Amyloid가설

What happens in the brain in Alzheimer's disease?



Beta-Amyloid가설



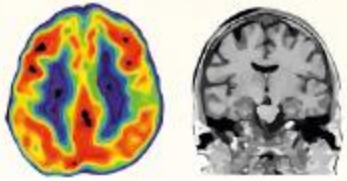
알츠하이머 Beta-Amyloid 진단

Progressive Brain Changes:

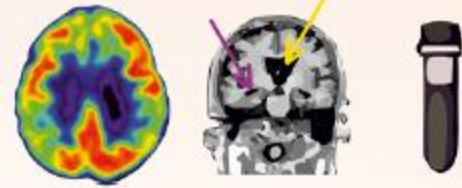
↑CSF *tau*, ↓CSF A β , Neuroinflammation, Synapse loss, Metabolic defects, Neurodegeneration, Neuronal hyperexcitability, Network dysfunction

Diagnostic Tools (A, current; B, future) + risk factors (*APOE* ϵ 4)

A. Brain Imaging Tests (PET, MRI)



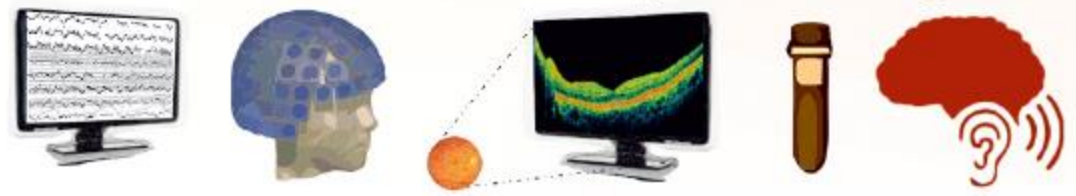
PET, MRI
Fluid Biomarkers



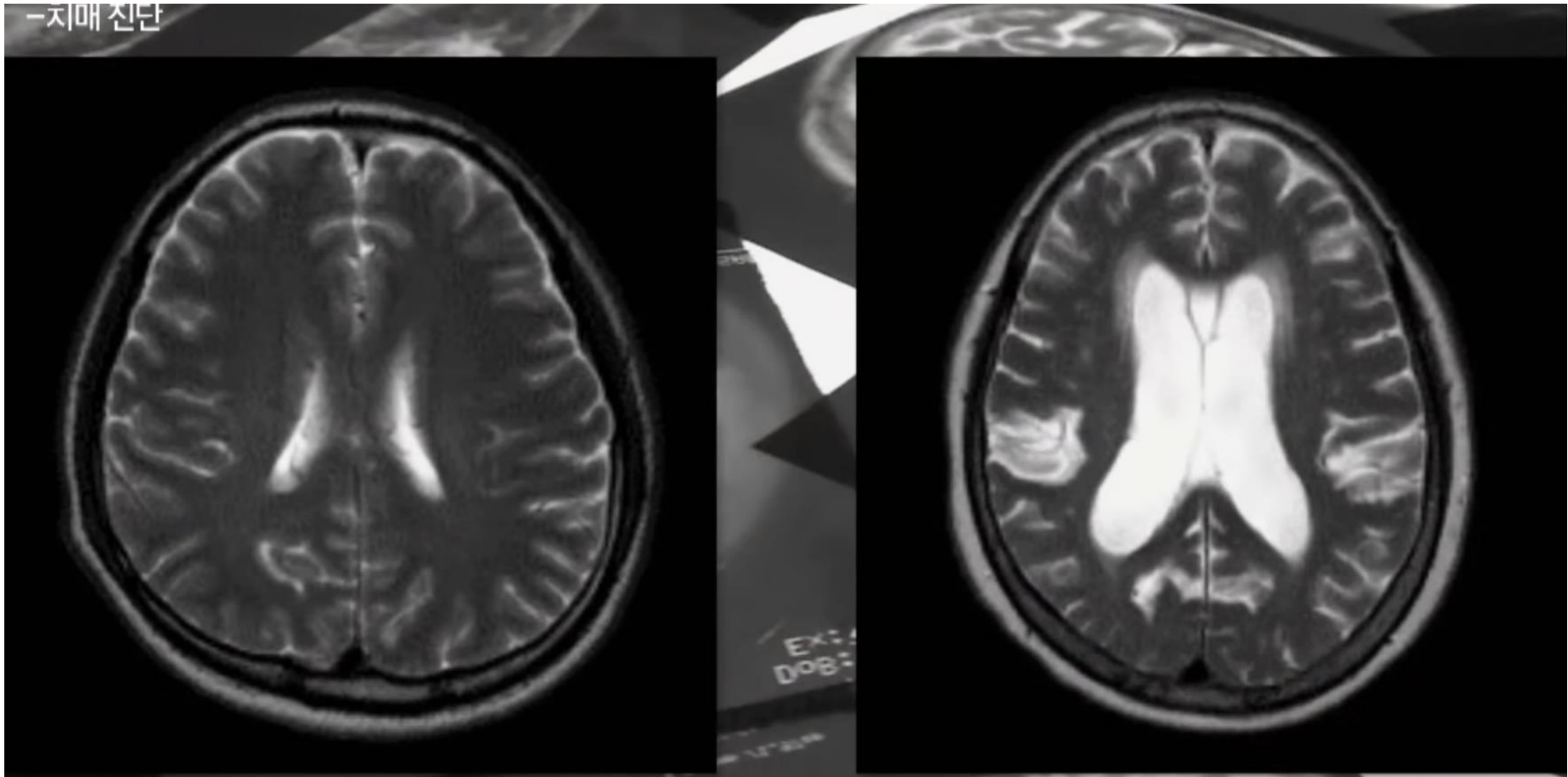
PET, MRI, Fluid Biomarkers, Neuropsychological Tests



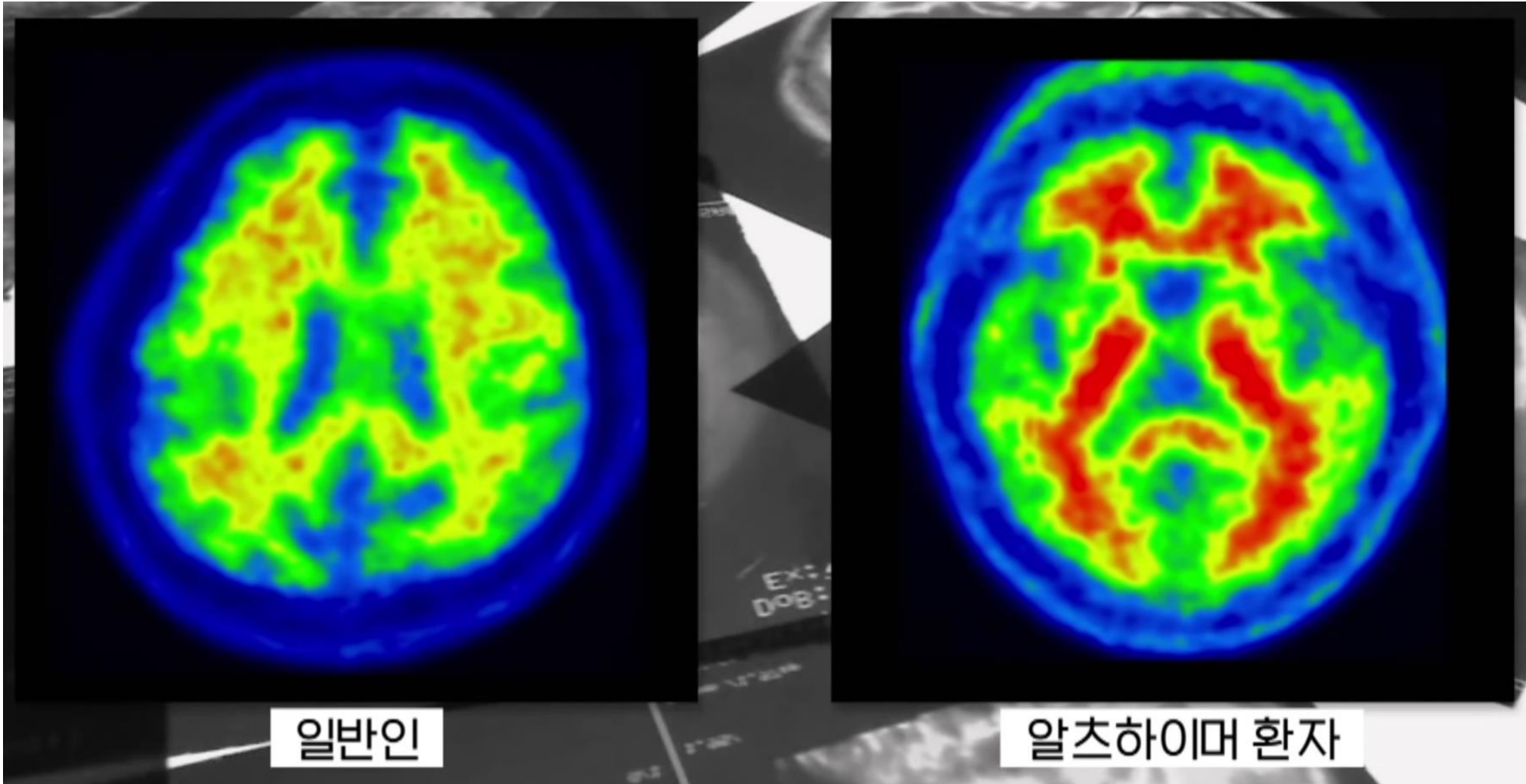
B. EEG, MEG, OCT, novel plasma biomarkers
Deficits in Central Auditory Processing



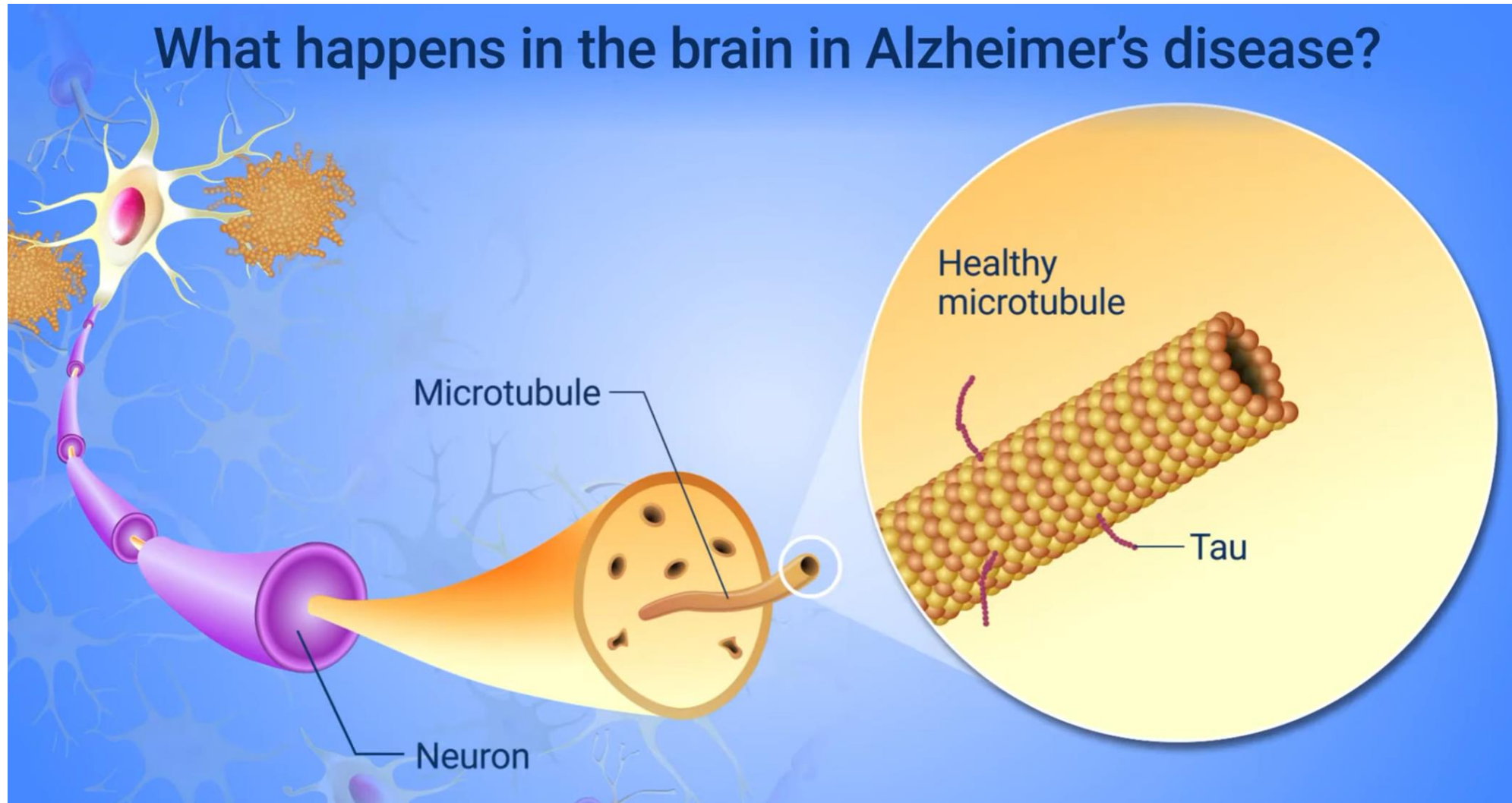
알츠하이머 진단-PET/MRI



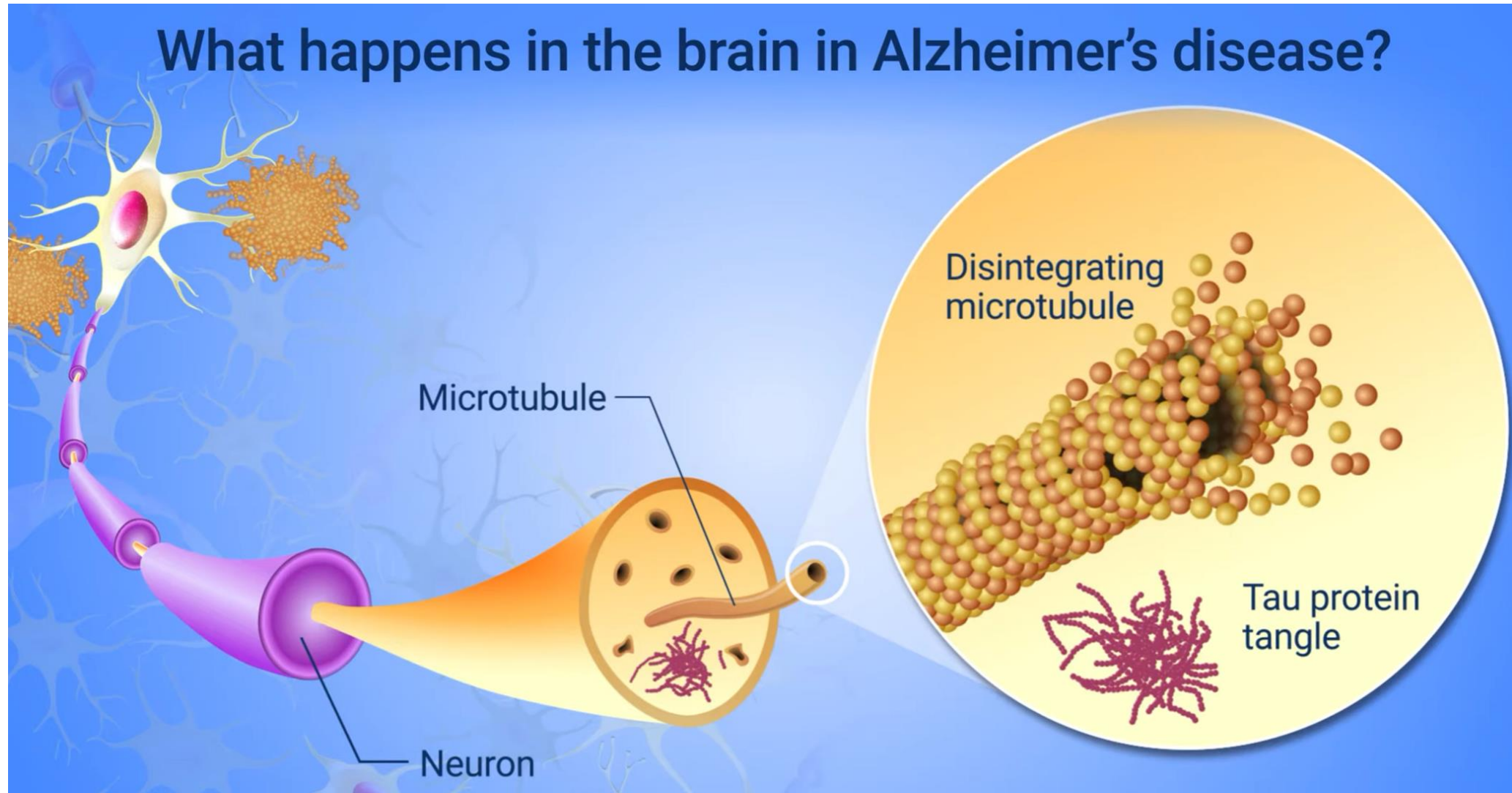
베타아밀로이드 단백질 PET



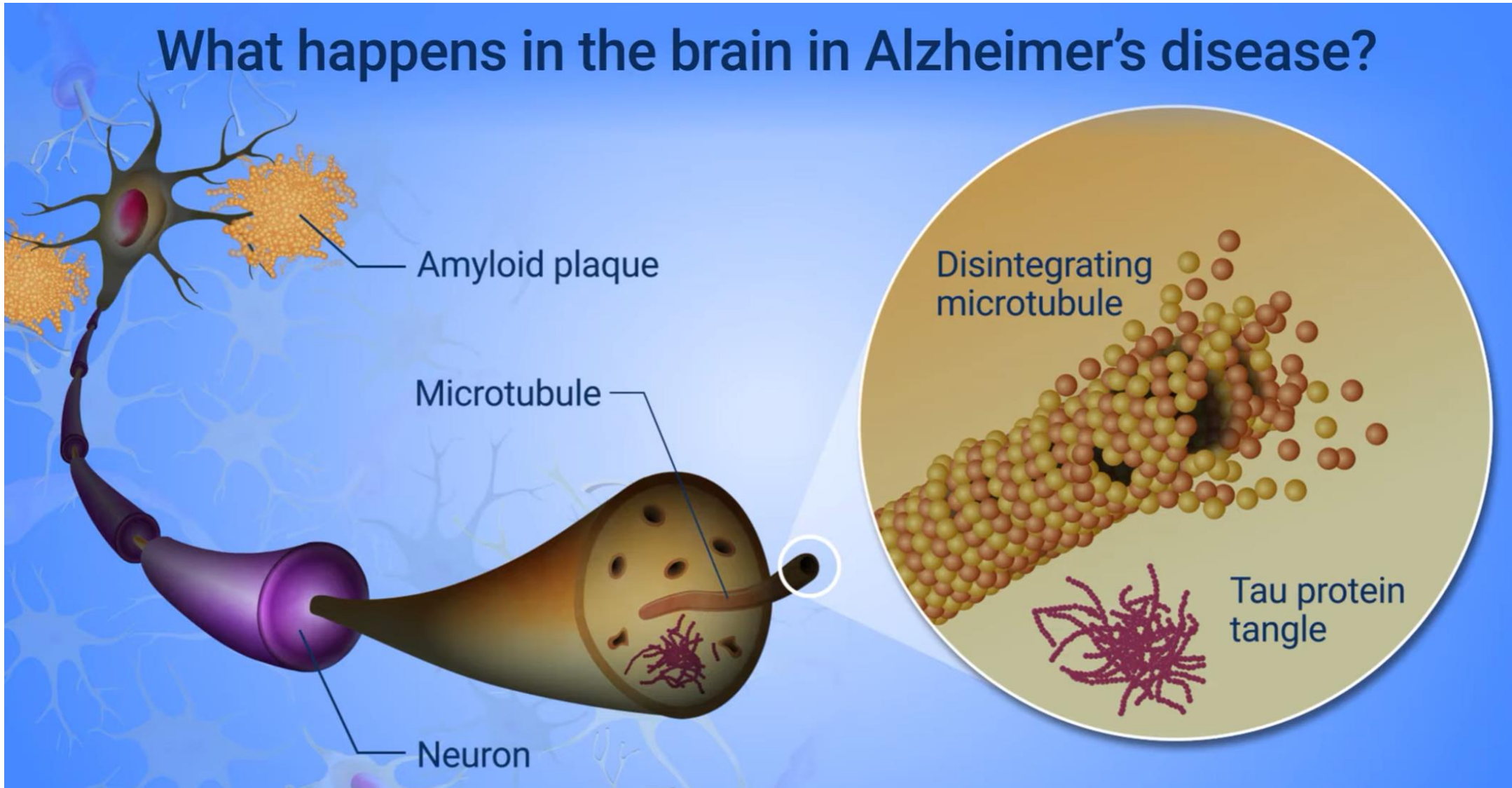
Tau & Tangle 가설



Tau & Tangle 가설

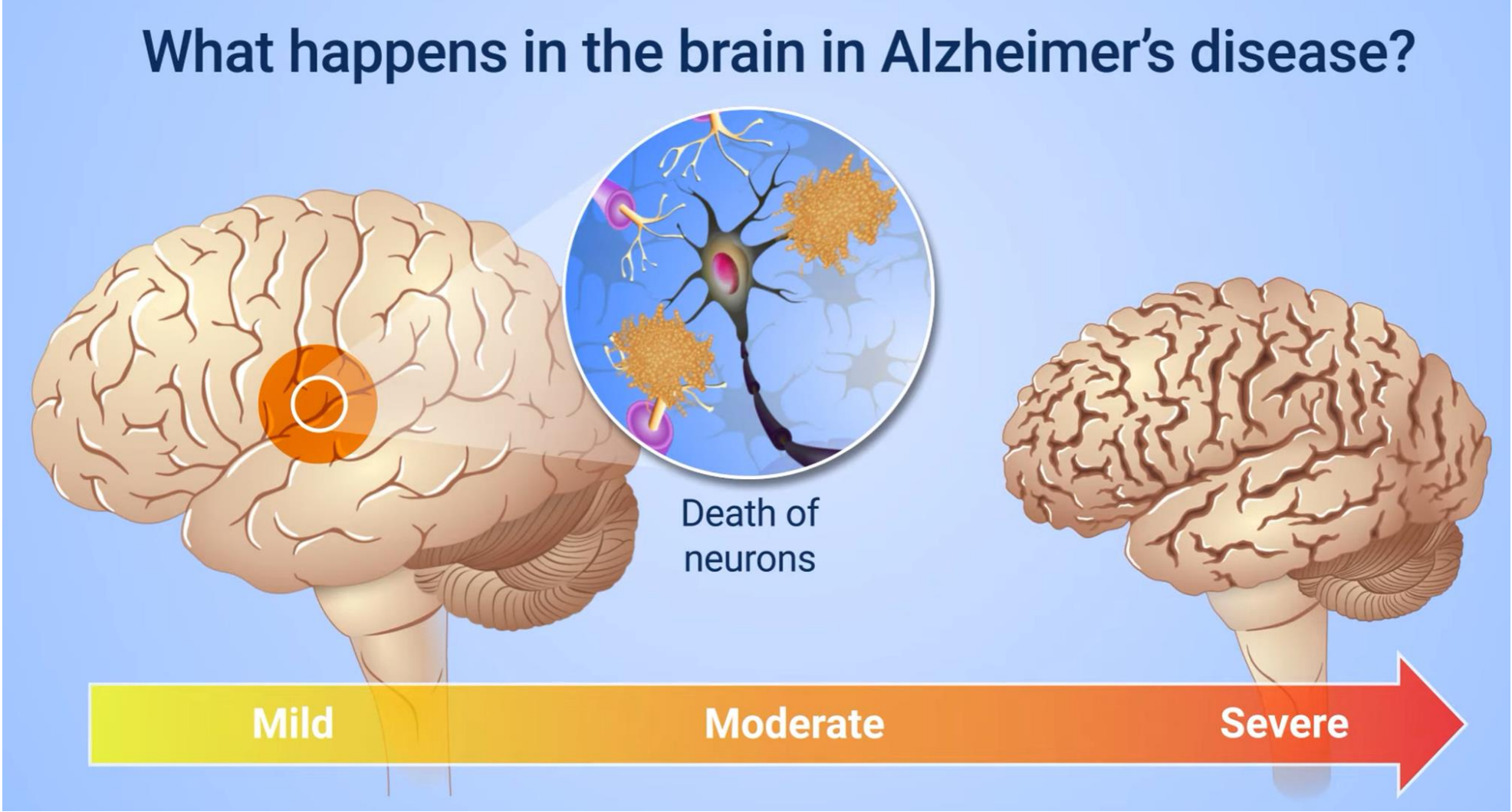


Beta-Amyloid, Tau & Tangle 가설

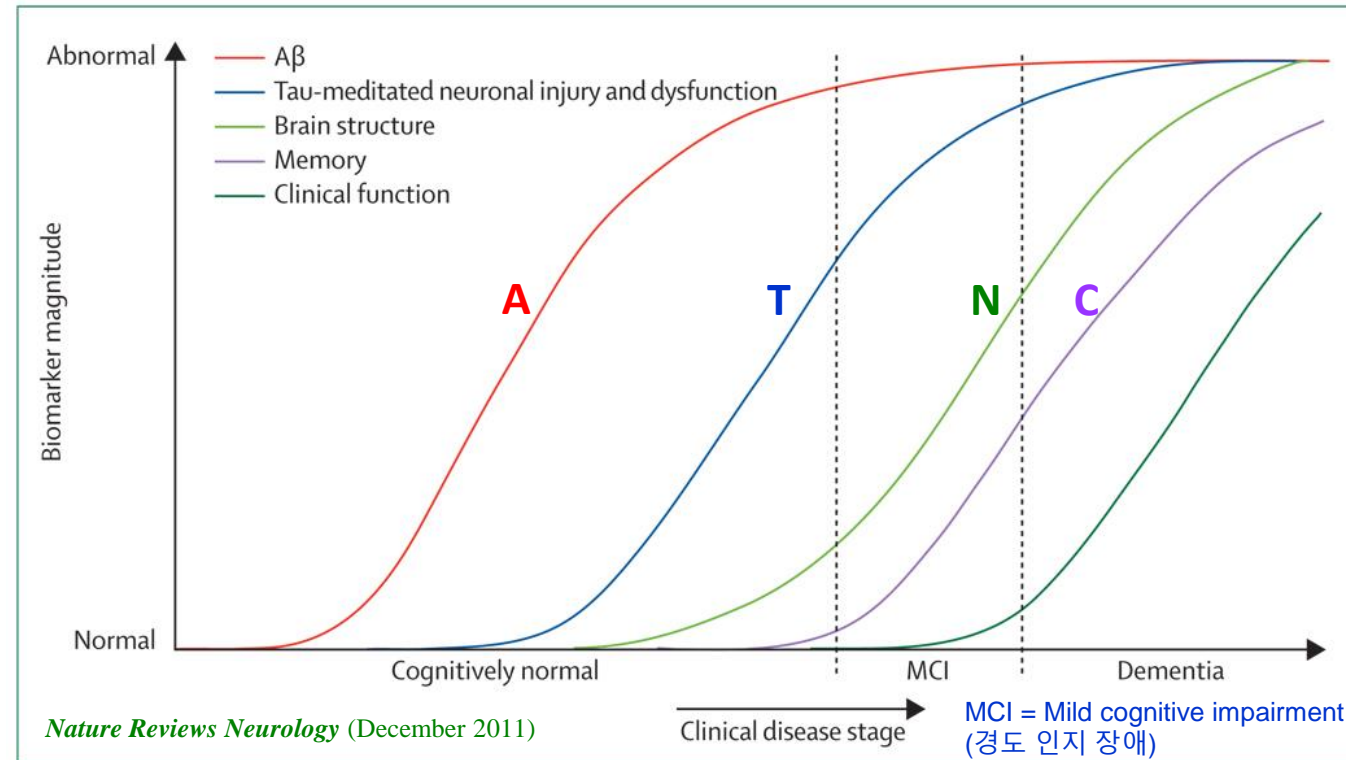


Beta-Amyloid, Tau & Tangle 가설

What happens in the brain in Alzheimer's disease?



Dynamic biomarkers of the Alzheimer's pathological cascade

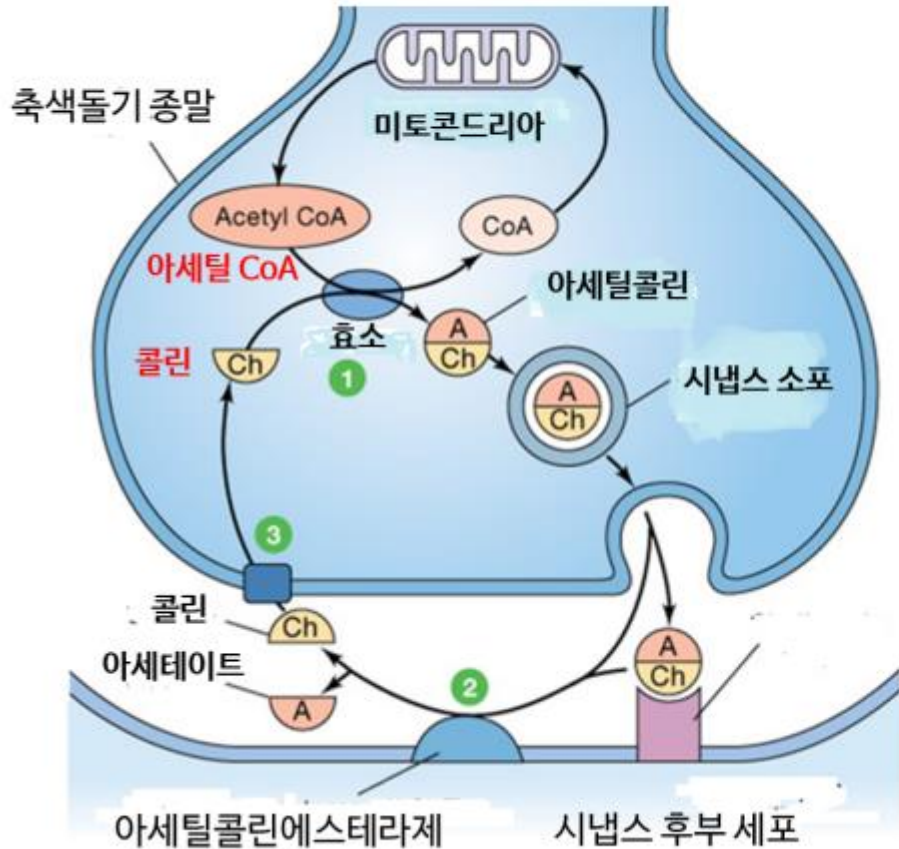


- Aβ is identified by CSF Aβ₄₂ or PET amyloid imaging.
- Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET.
- Brain structure is measured by use of structural MRI.

[Chronology] Aβ aggregation → Tau deposition → Neuronal death → Cognitive deficits

아세틸 콜린가설

뇌신경세포에서 아세틸콜린의 합성과 분해



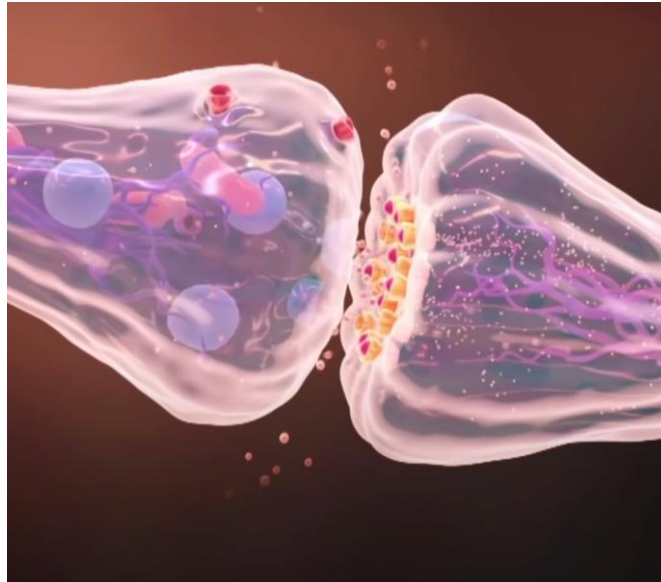
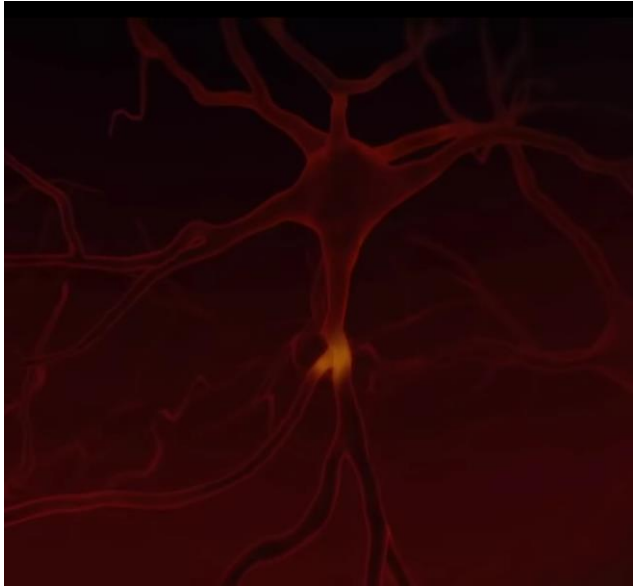
1 아세틸콜린은 콜린과 아세틸 CoA로부터 합성된다

2 아세틸콜린은 시냅스에서 아세틸콜린 에스테라제 효소에 의해 빠르게 분해된다

3 분해된 콜린은 다시 축색돌기 종말로 돌아가 아세틸콜린을 합성하는데 사용된다

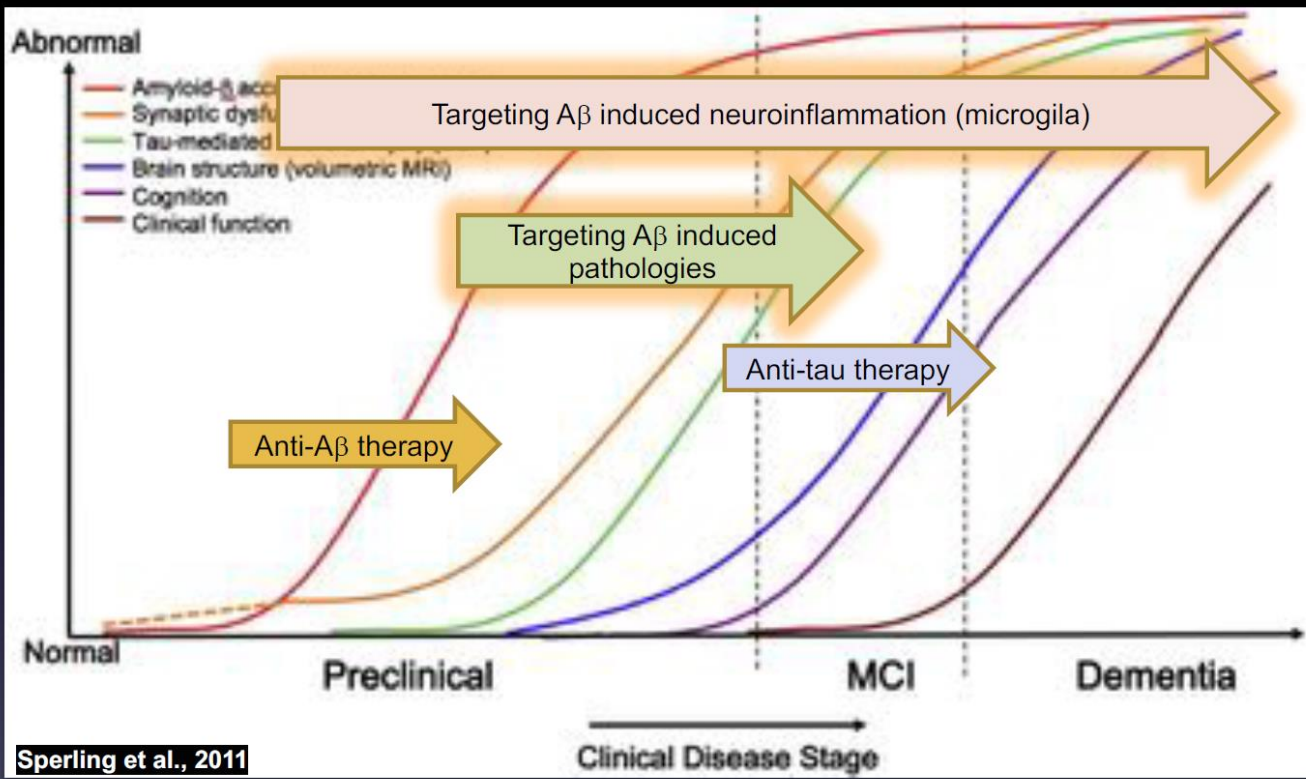
→ 억제 → 치매완화

알츠하이머 신약개발 동향



적기치료 중요

Progression of Alzheimer's disease pathology

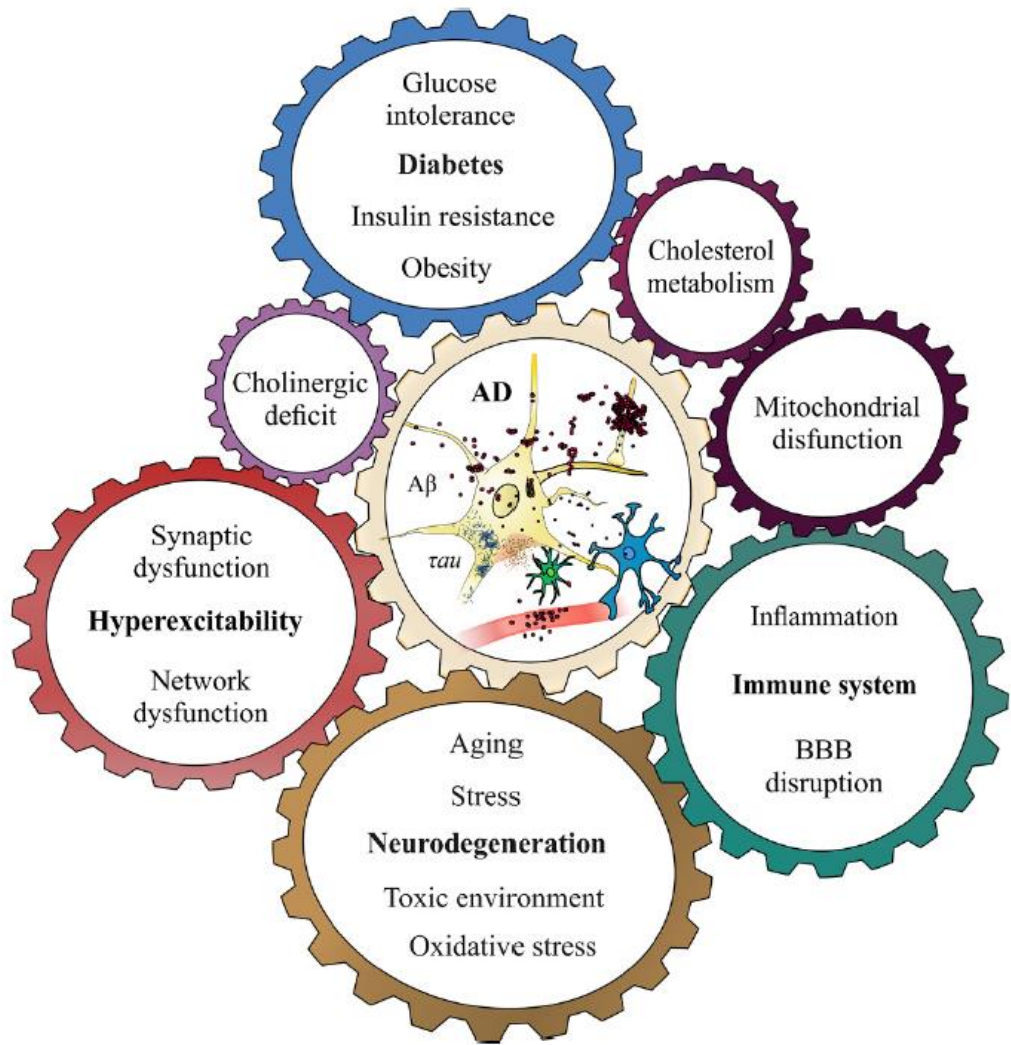


Three pillars of AD pathology: Amyloid, Tangles, Neuroinflammation

임상단계: Clinical Trial Phases

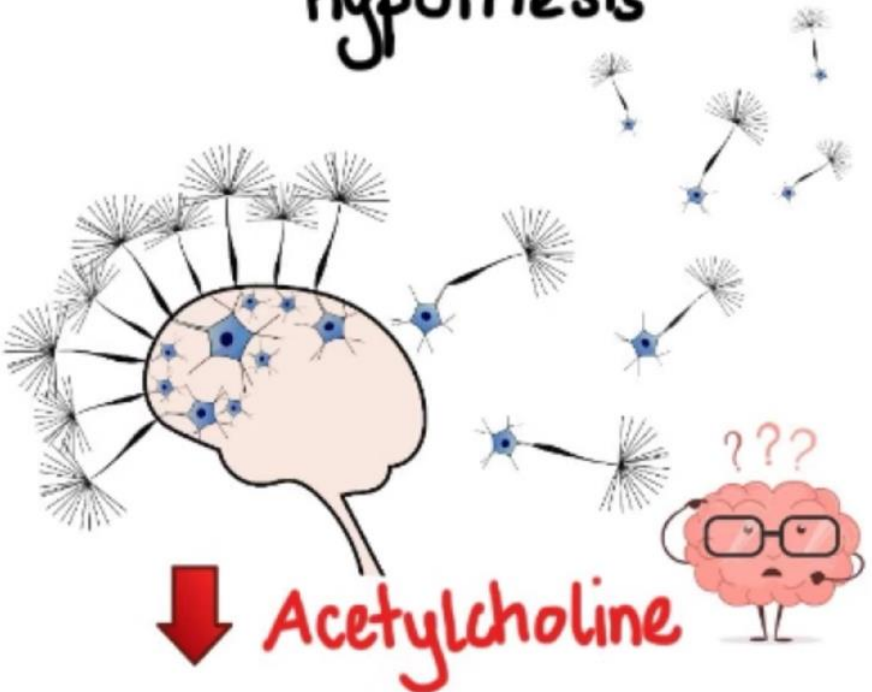
Phase	Subjects	Placebo	Goal	Duration
I	10, often healthy	No	Is it safe? What dose/duration?	days to weeks
II	100 patients	Yes	Is it beneficial? Are there side effects?	months
III	1000 patients	Yes	Overall benefit/risk?	year(s)

알츠하이머 원인 인자들

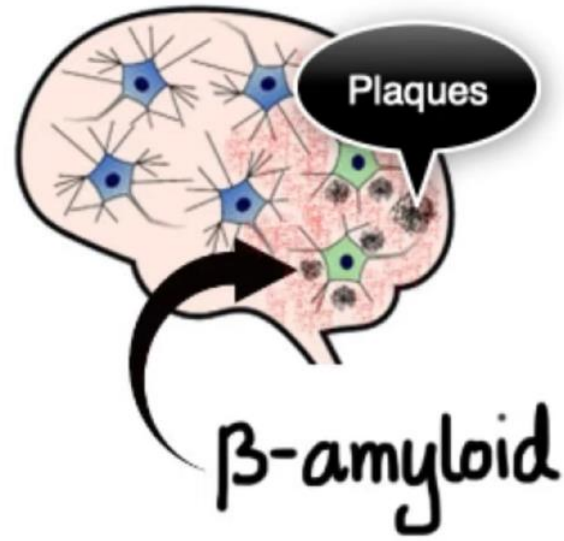


신약개발 표적들

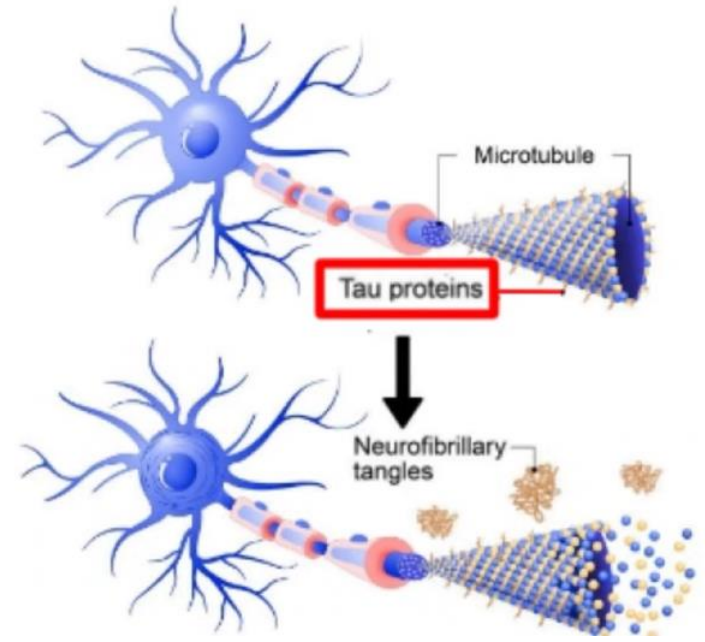
Cholinergic hypothesis



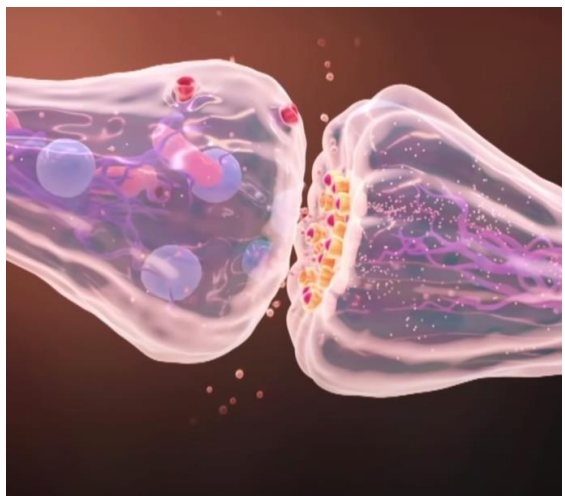
Amyloid hypothesis



Tau hypothesis

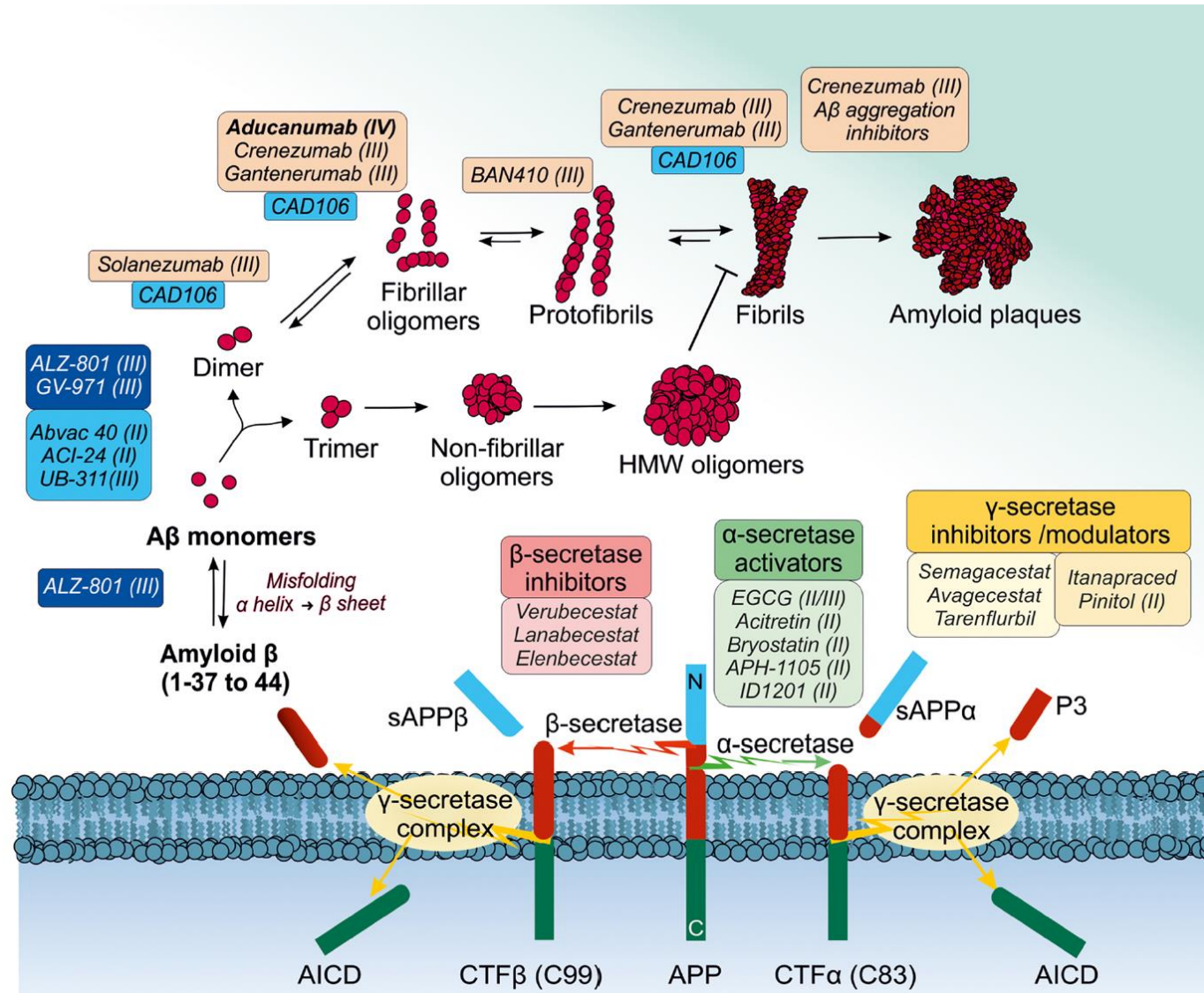


Acethyl Cholinesterase → 완화제



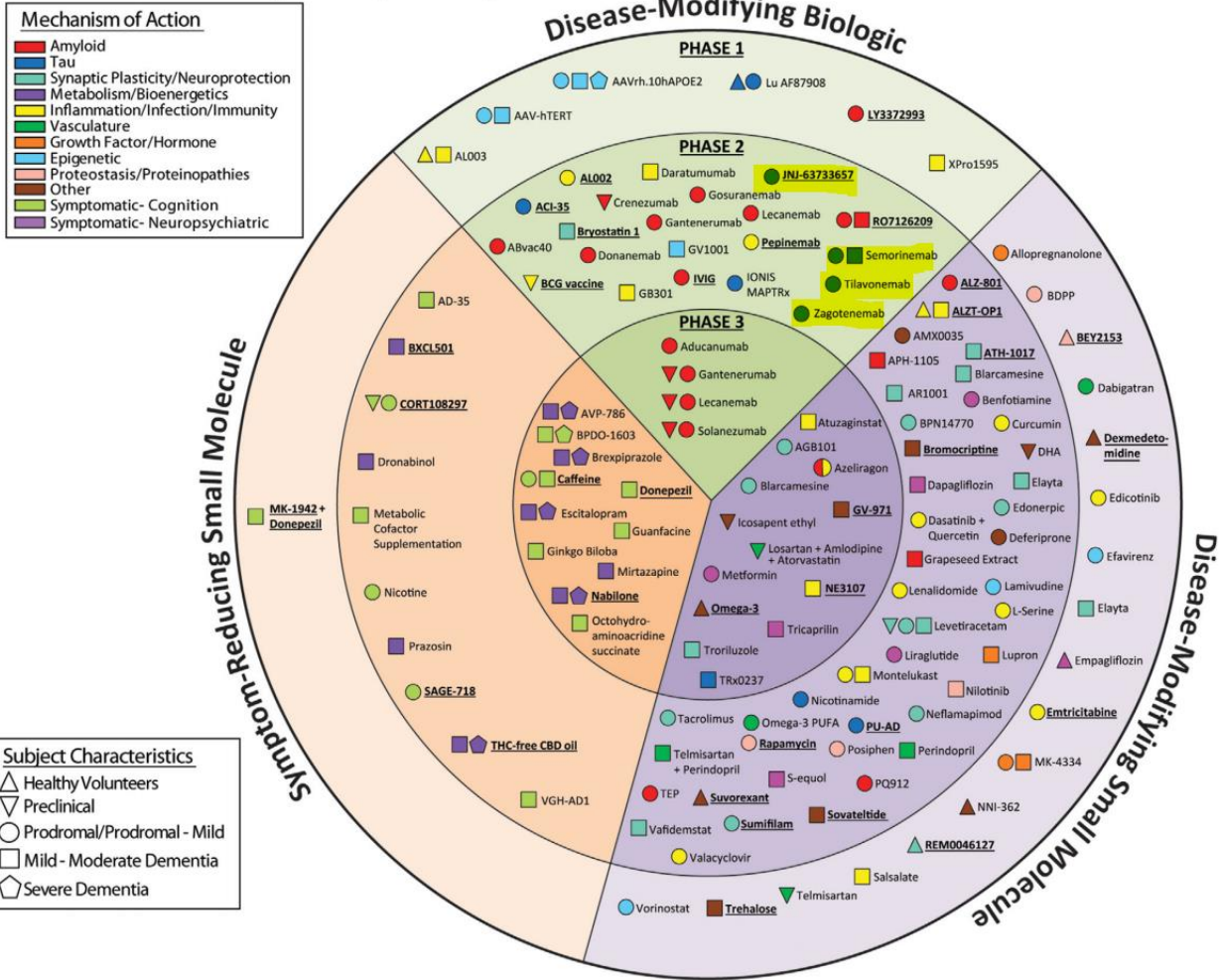
Name	Action	FDA approval for AD
Donepezil (Aricept)	Cholinesterase inhibitor	mild, moderate, severe
Rivastigmine (Exelon)	Cholinesterase inhibitor	mild, moderate, severe
Galantamine (Razadyne)	Cholinesterase inhibitor	mild, moderate
Memantine (Namenda)	Glutamate antagonist	moderate, severe
Donepezil + Memantine (Namzaric)	combination	moderate, severe

Beta-Amyloid 생성 및 Oligomer 형성 억제 표적



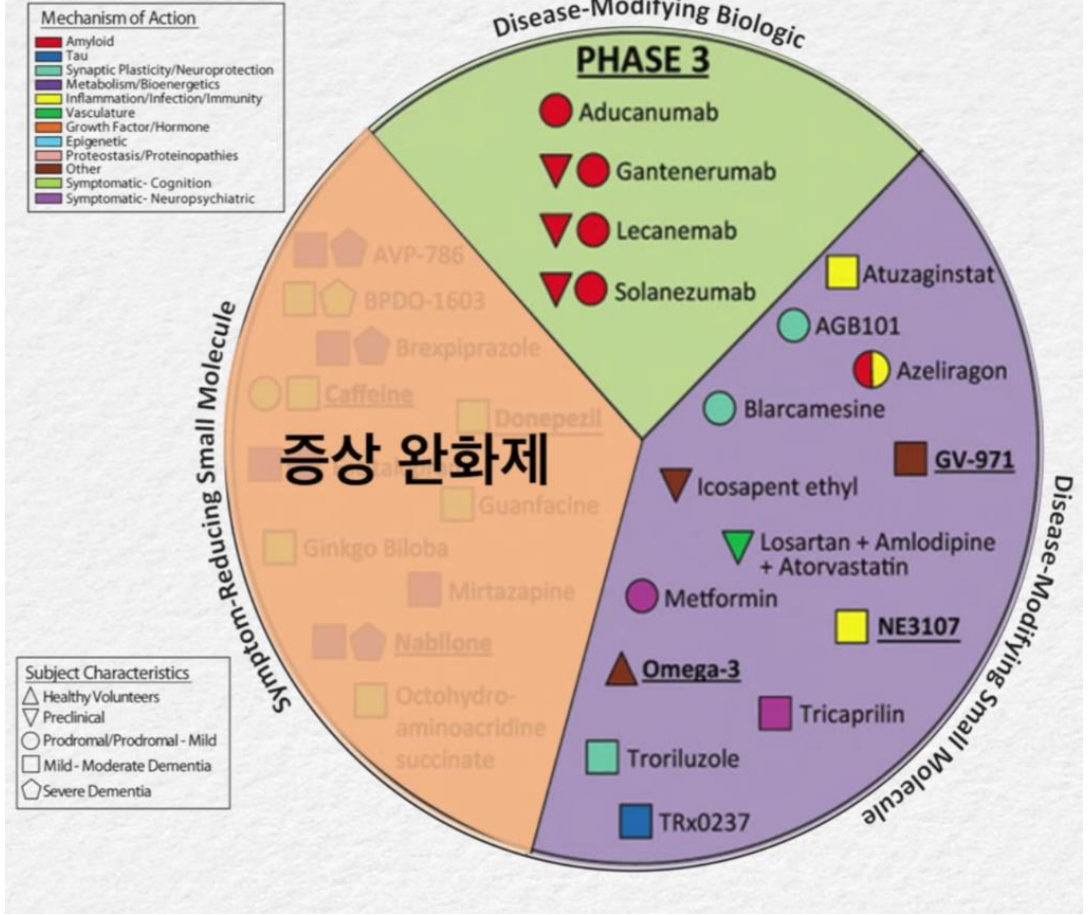
알츠하이머 약물치료: Aducanumab & 3상 중 치료제

2021 Alzheimer's Drug Development Pipeline

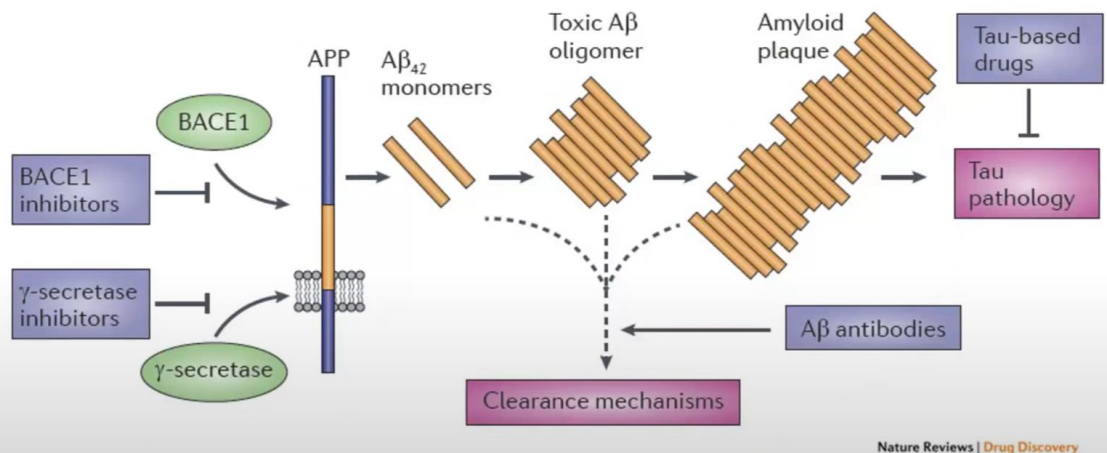


임상 3상 중인 치료제들

2021 Alzheimer's Drug Development Pipeline



알츠하이머 약물치료 → 23%환자 효과



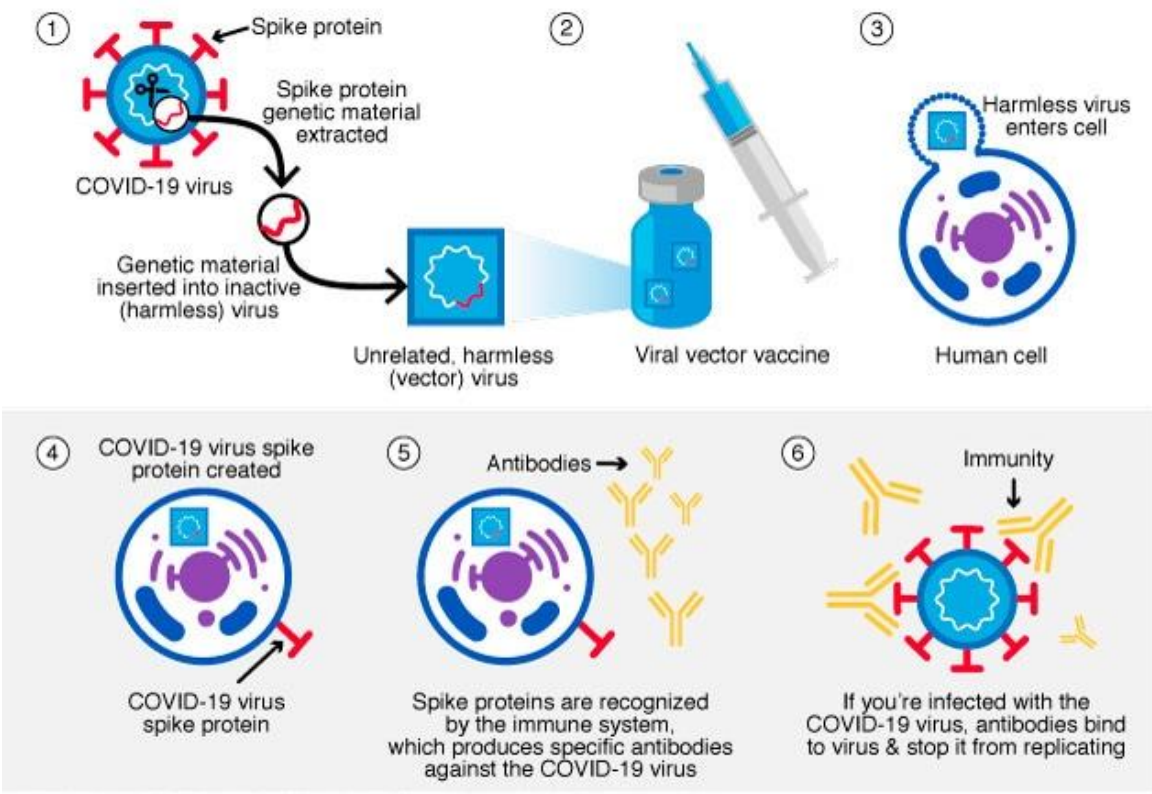
Mullard, Nature Reviews, 2012

아두카누맙 임상결과



출처 : Nature. 2016

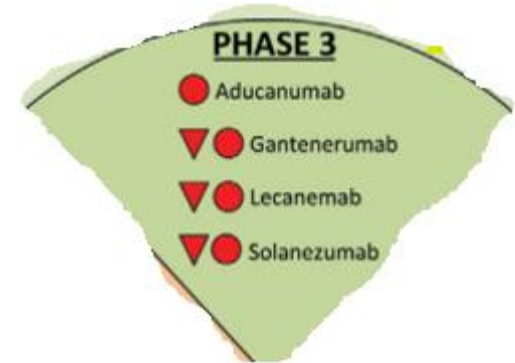
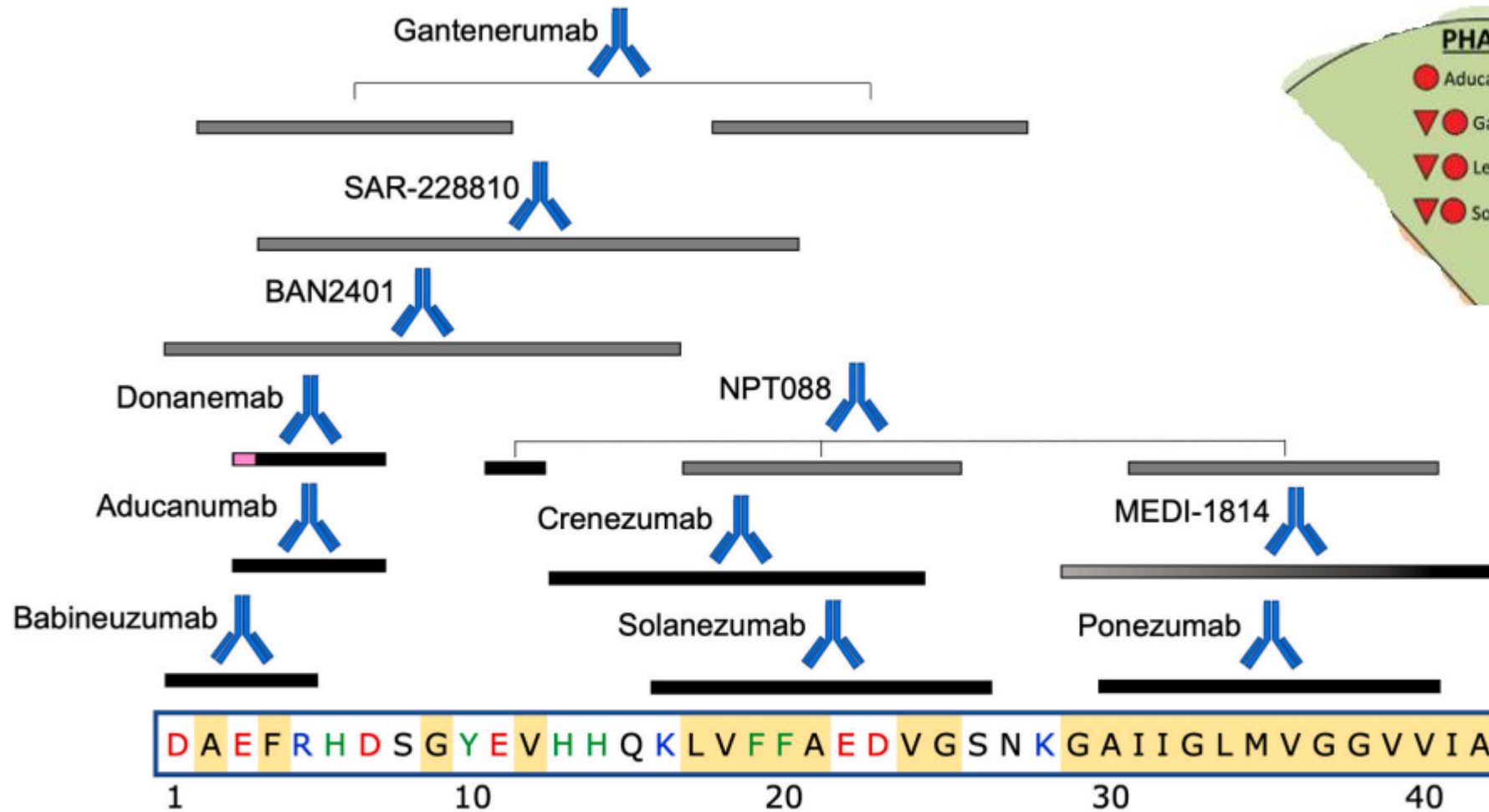
항체란? COVID-19 Vaccine → 항체 형성



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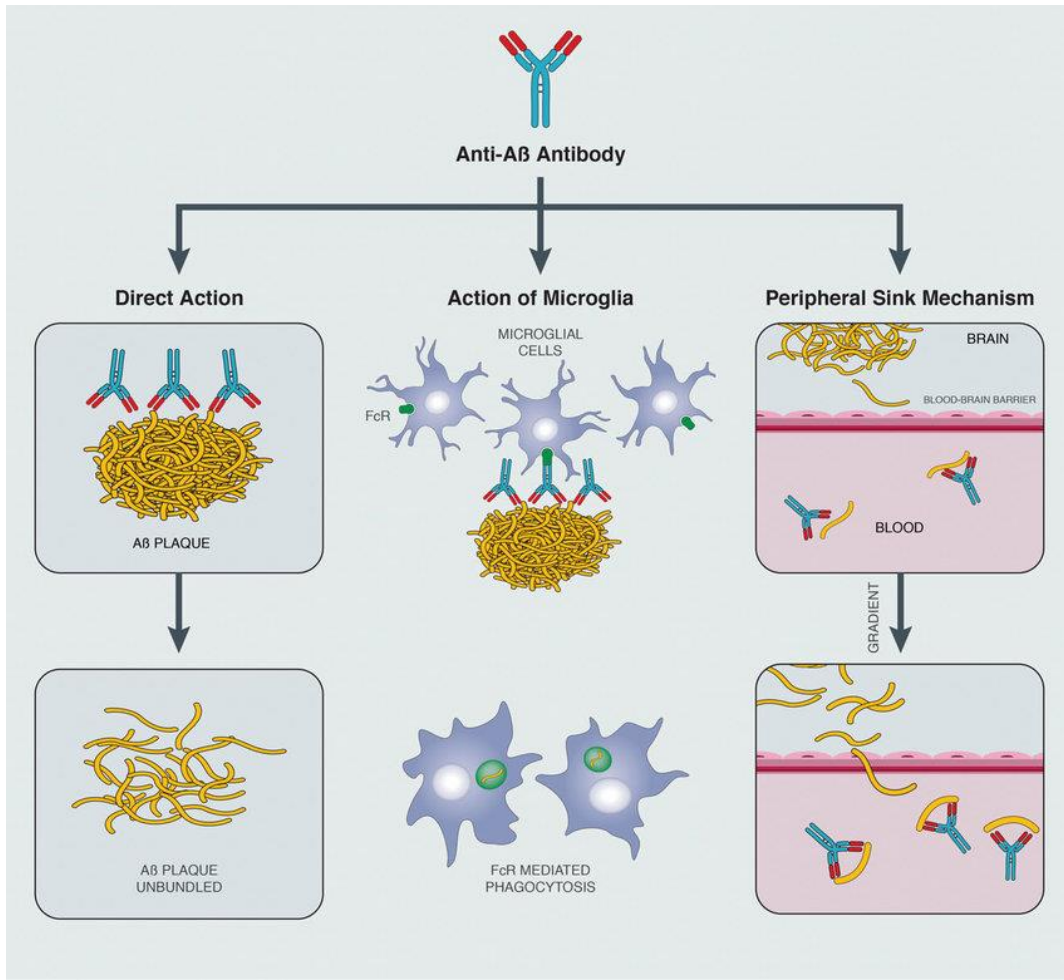


Beta-Amyloid 항체 신약연구

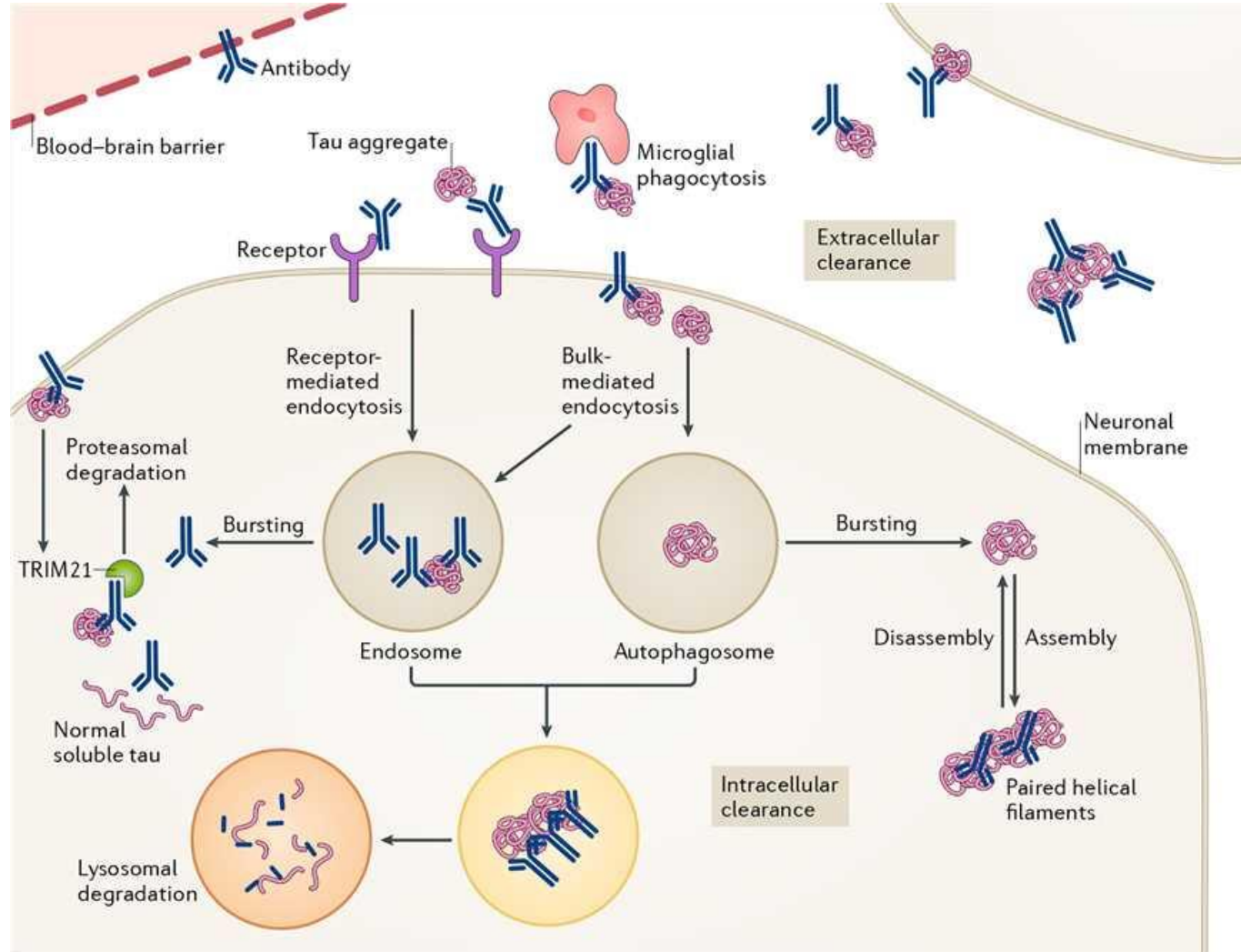


아두카누맙 작용기적

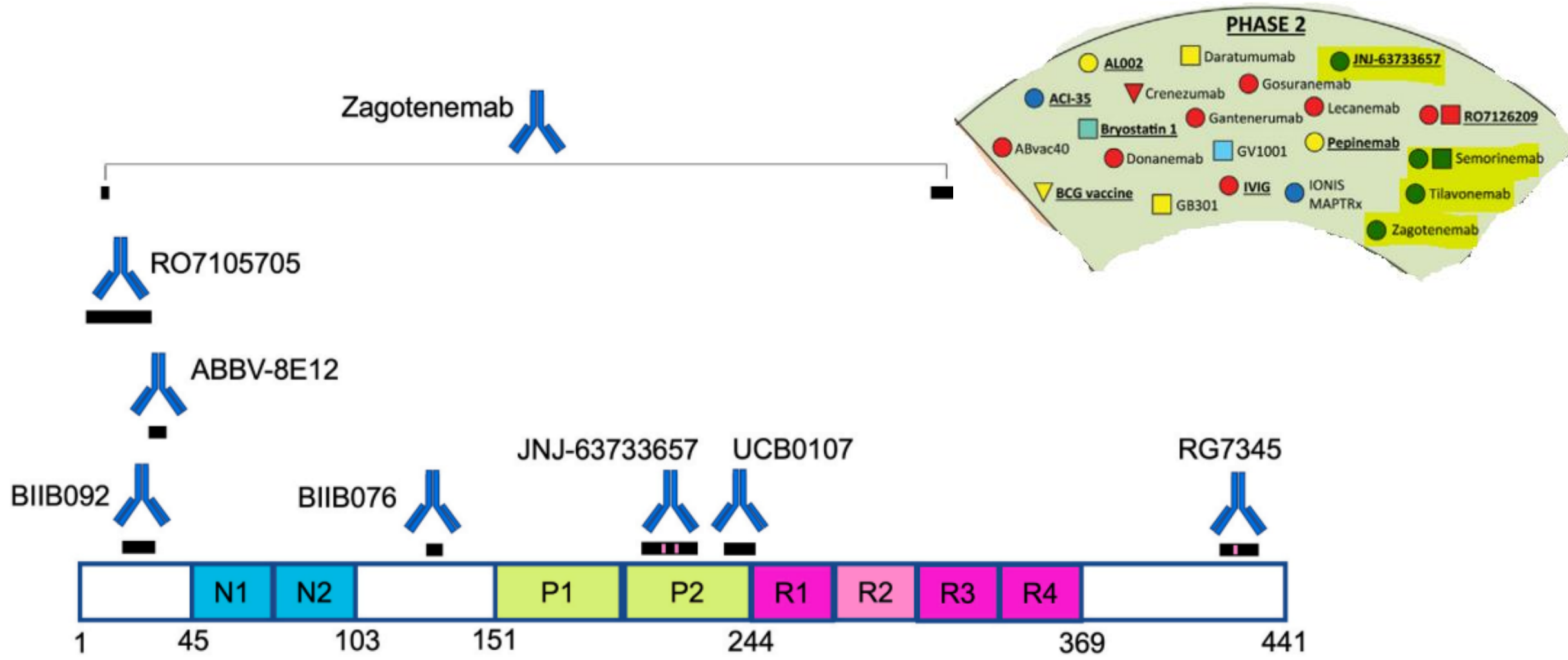
아두카누맙(아두헴)의 작용기전



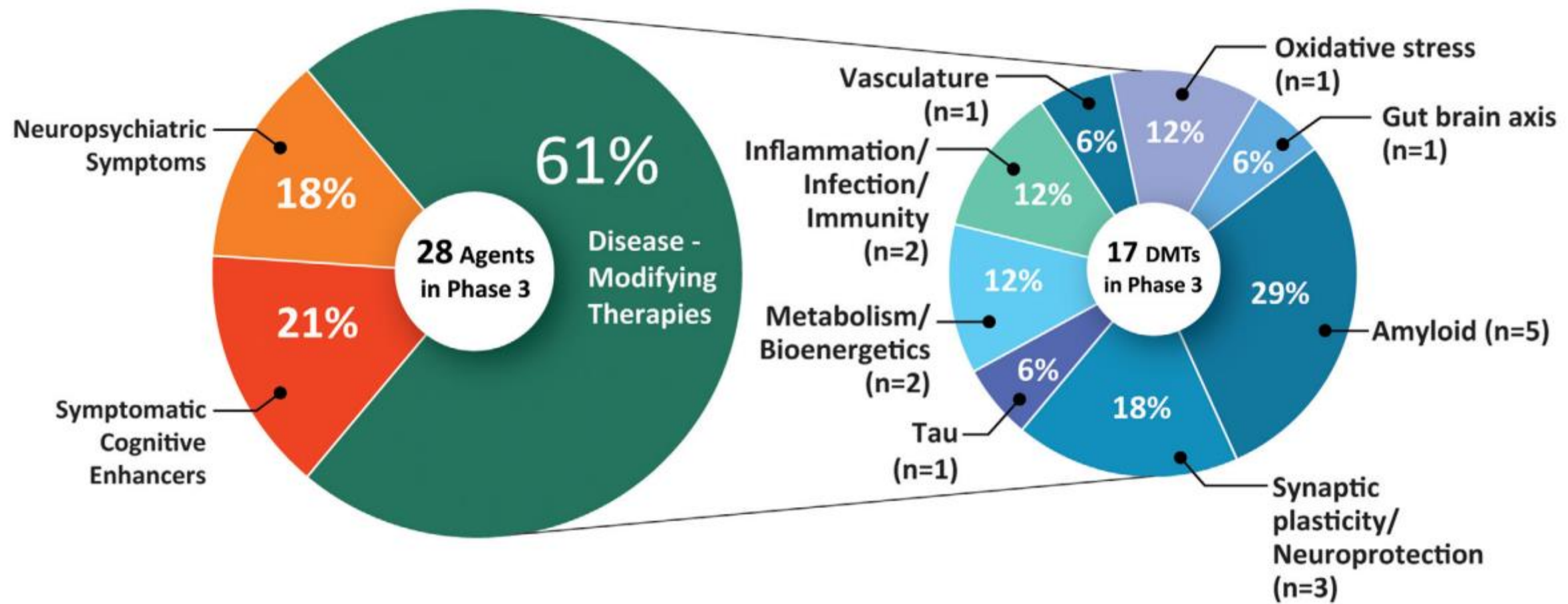
Tau 항체 치료제 기작



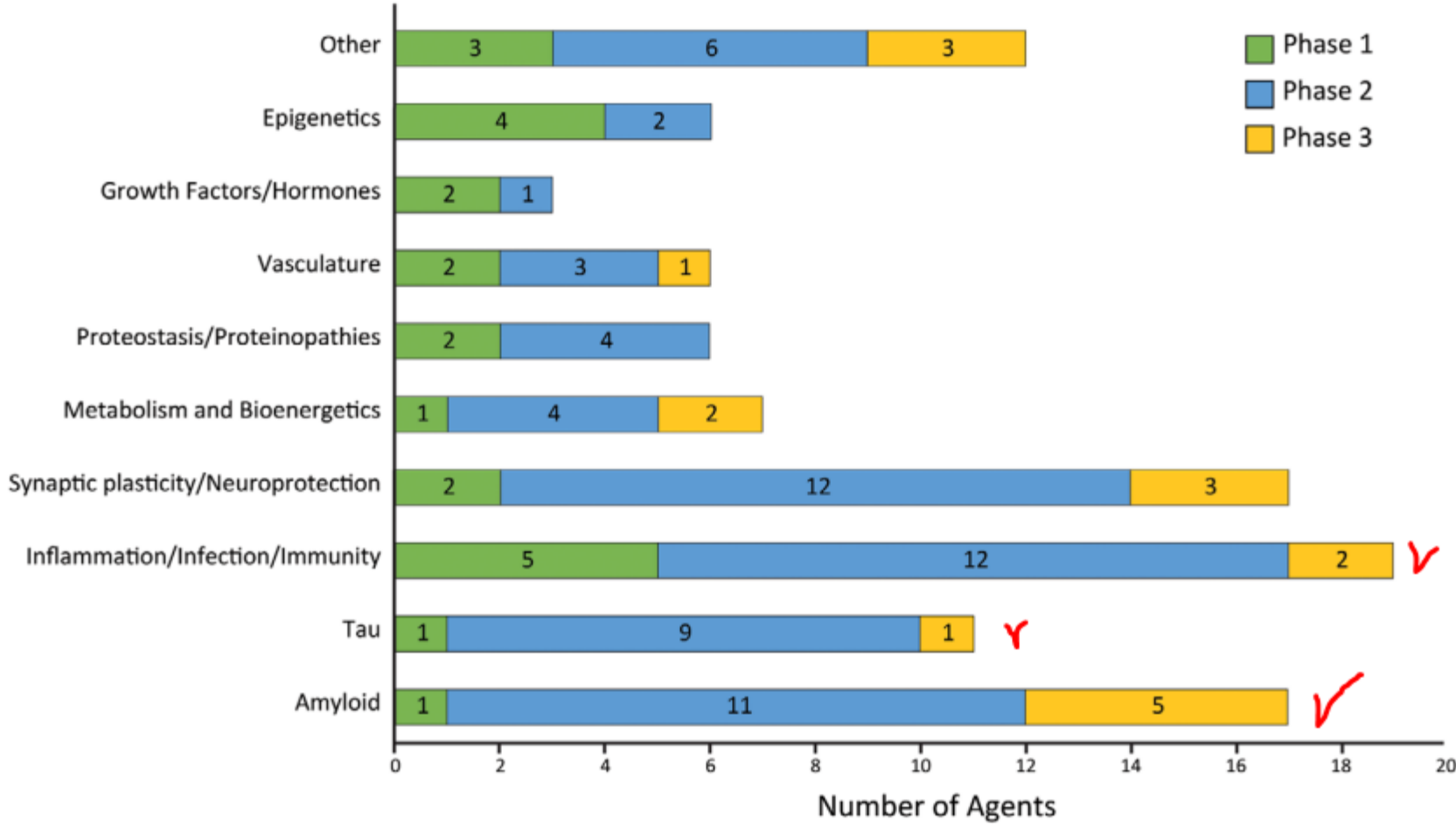
Tau 항체 신약연구



알츠하이머 약물치료: 3상 중 치료제



알츠하이머 약물치료 현황: Mechanism of Action



알츠하이머 약물치료 현황: Summary

- **1세대 약물(Symptomatic cognitive enhancer):** 아세틸콜린 분해효소 억제제(Acetylcholinesterase inhibitors), NMDA 수용체 길항제(NMDA receptor antagonist)
 - 부작용: 구역감, 설사, 식욕감퇴, 체중 감소, 어지러움, 근육경련
 - 효능: 일시적으로 인지기능 장애 증상의 완화를 보이지만, 병의 진행에 는 영향이 없음
- **2세대 약물(Disease-modifying A β -targeting agent):** 아두헬름(Aduhelm), 레카네맵(BAN2401)?, 도나네맵?
 - 아두헬름은 인지개선 기능을 뚜렷하게 보여주지 못함 (초기환자에 23%효과)
 - 아두헬름은 1회 **정맥주사**하는 데 드는 비용이 약 480만원(= 연 6,230만원)
- **3세대 약물:** 베타아밀로이드 항체? 타우항체? → 고가 정맥주사
염증억제제? ApoE? 미토콘드리아? 장내 미생물?
**원하는 치료제는: 경구복용 가능한 저분자 약물 → 환자복용편이
저렴한 가격 → GENOSCO 전략**



알츠하이머 비약물 예방프로그램: **Finger Program**

1. 유산소 운동: 걷기, 등산
2. 인지강화 운동: 책보기, 글쓰기 등
3. 위험인자 관리: 당뇨, 고혈압, 고지혈증
4. 사회성 강화: 가족과 이야기하기
5. 식의 조절: 항산화 식물

→ 문지방을 벗어나자!!! 부지런하자!!!

알츠하이머 비약물 예방: **Finger Program**



Don't smoke



Keep your body and your mind active



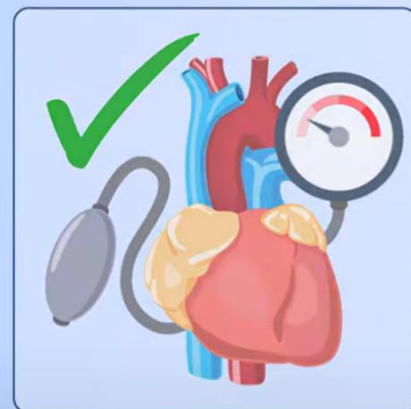
Stay in touch with family and friends



Eat a healthy diet



Maintain healthy weight



Control high blood pressure

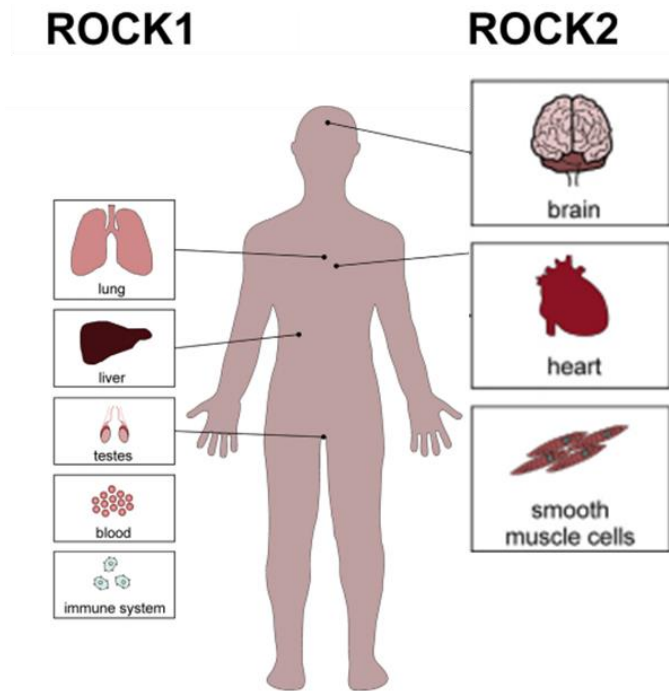


Drink alcohol in moderation



Drink coffee in moderation

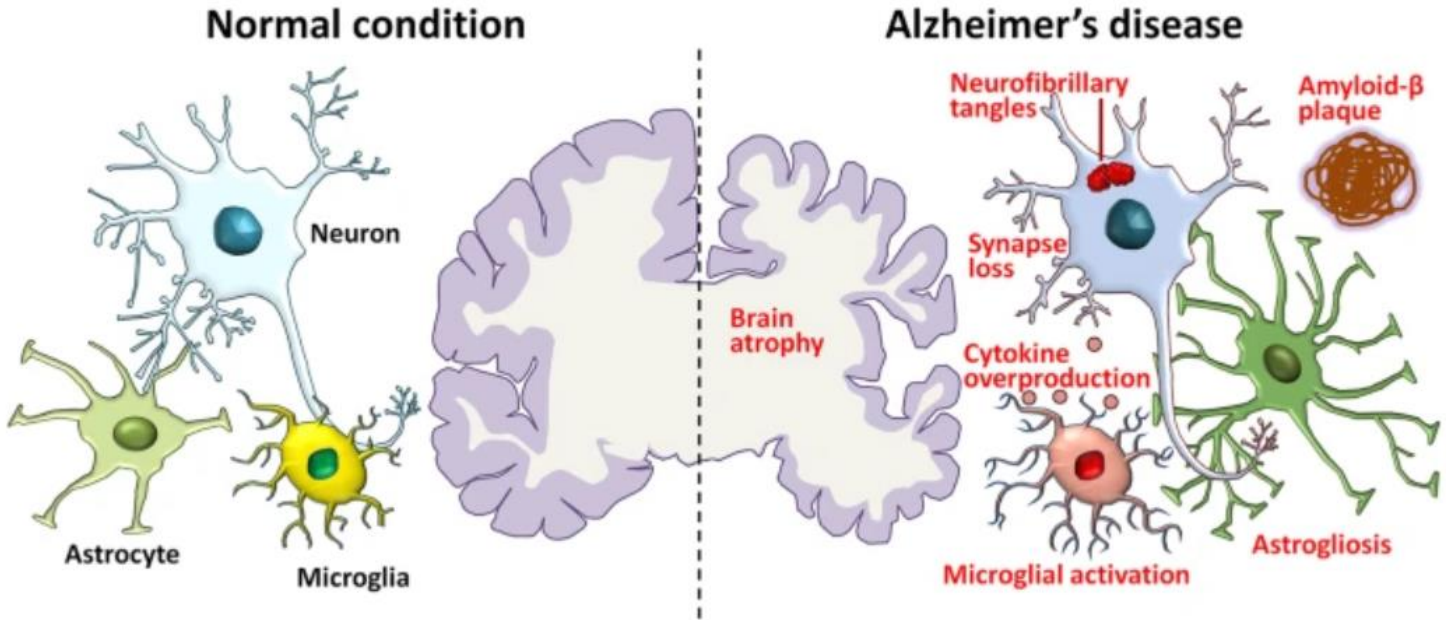
GENOSCO's Approach: ROCK2억제제-Rock and Roll Project



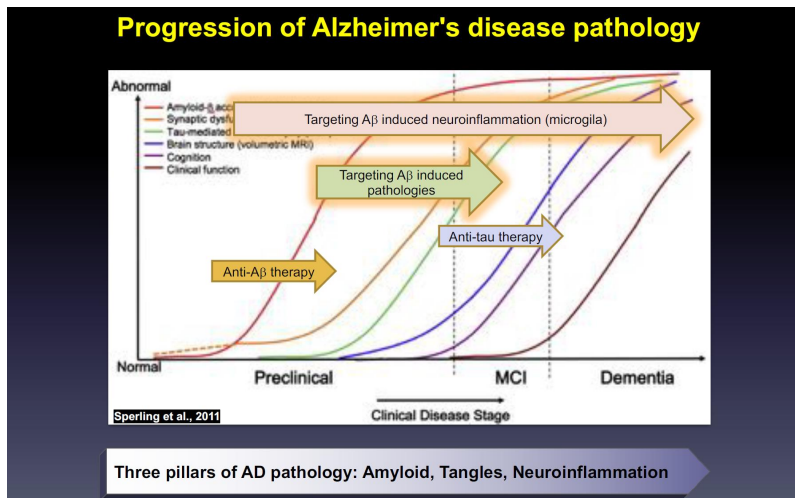
Summary

APP/PS1 Tg mice treated with **ROCK2 selective inhibitor** showed reduced numbers of **A β 1-42 plaque** and of **p-Tau and BACE** positive cells, increased expression of synapse-associated proteins and neurotrophic factors and recovered to some extent for the 'space learning and memory impairment'. **ROCK2i** also plays roles in anti-inflammation and promoting neurite outgrowth.

GENOSCO's Approach: ROCK2 Selective 억제제



- Extracellular A β plaques
- Intracellular tau tangles
- Loss of synapse
- Activation of microglia
- Overproduction of cytokines
- Astrogliosis



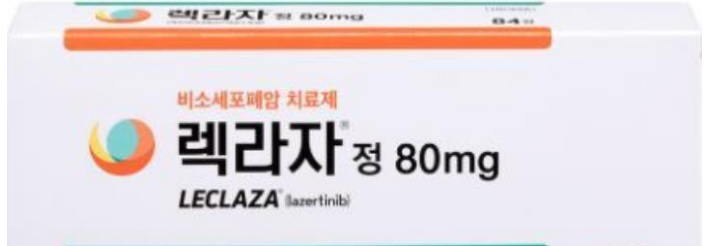
ROCK2i 억제제 성질

- 1, B-Amyloid 및 Tau 감소
- 2, 신경세포 자극인자 증가
- 3, 혈관손상 감소
- 4, 신경세포 성장활성화
- 5, 신경염증 감소
- 6, 혈관강화
- 7, BBB 통과

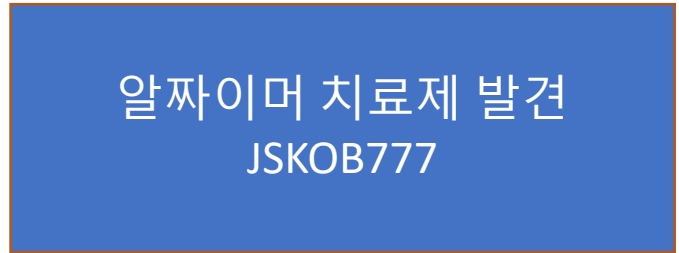
My hope and dream!!!



Anti-diabetic drug-Zemiglo 발견
대한민국 당뇨치료 주권 확보
2004



Anti-cancer drug-Leclaza 발견
대한민국 폐암치료 주권 확보
2014



Anti-AD drug-JSKOB777 발견
알츠하이머 치료주권을..
2024?



Yes, I can!!!

감사합니다

선후배님들!!! 알츠하이머 치료제 만드는 꿈을 저와 같이 ^-^
Let's dream together!!! Dream ★ will come true!!!

If one person dreams a dream, it is but a dream.
**But if people dream that dream together, then it
becomes reality.**

-Genghis Kahn-