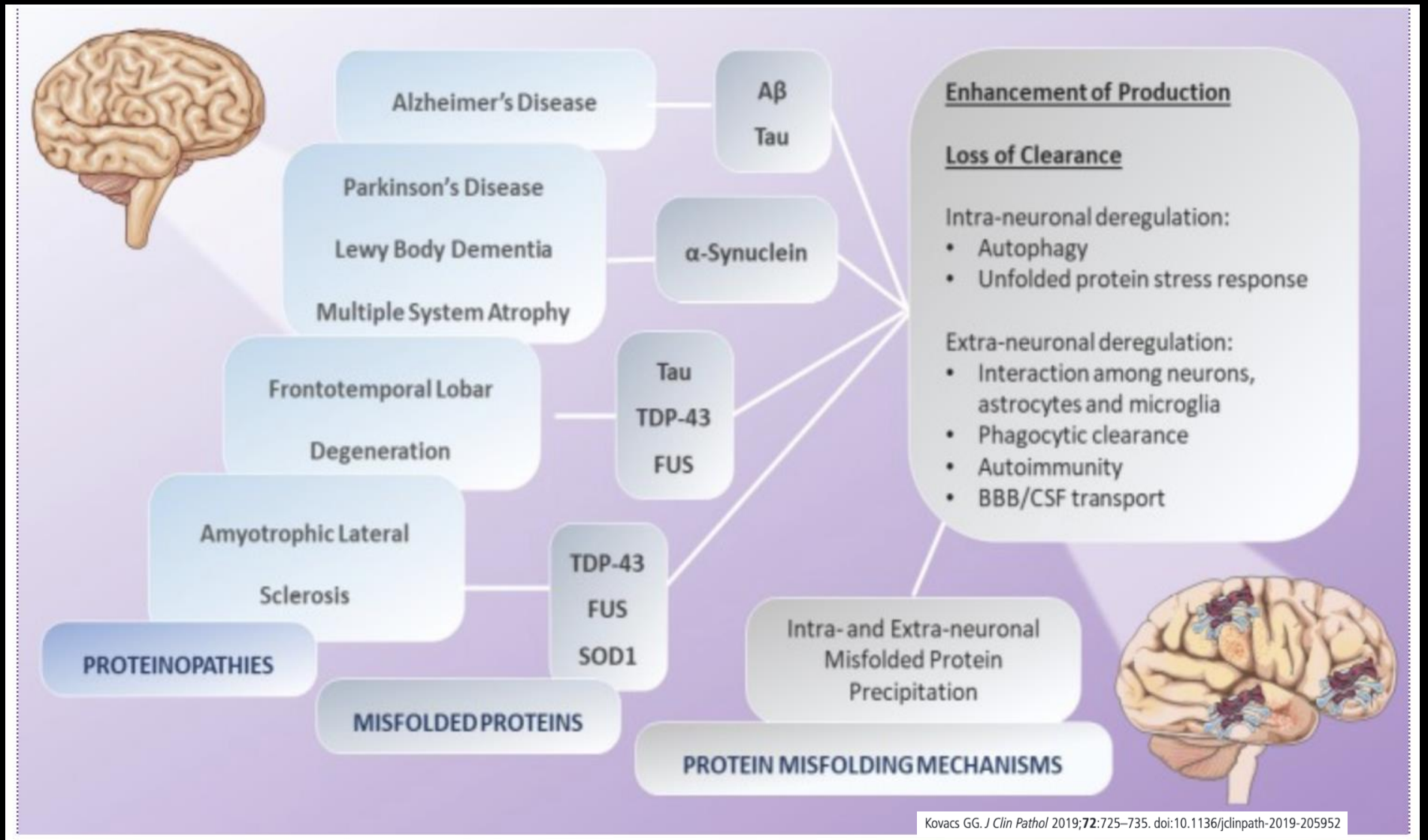
NEURODEGENERATIVE DISEASES

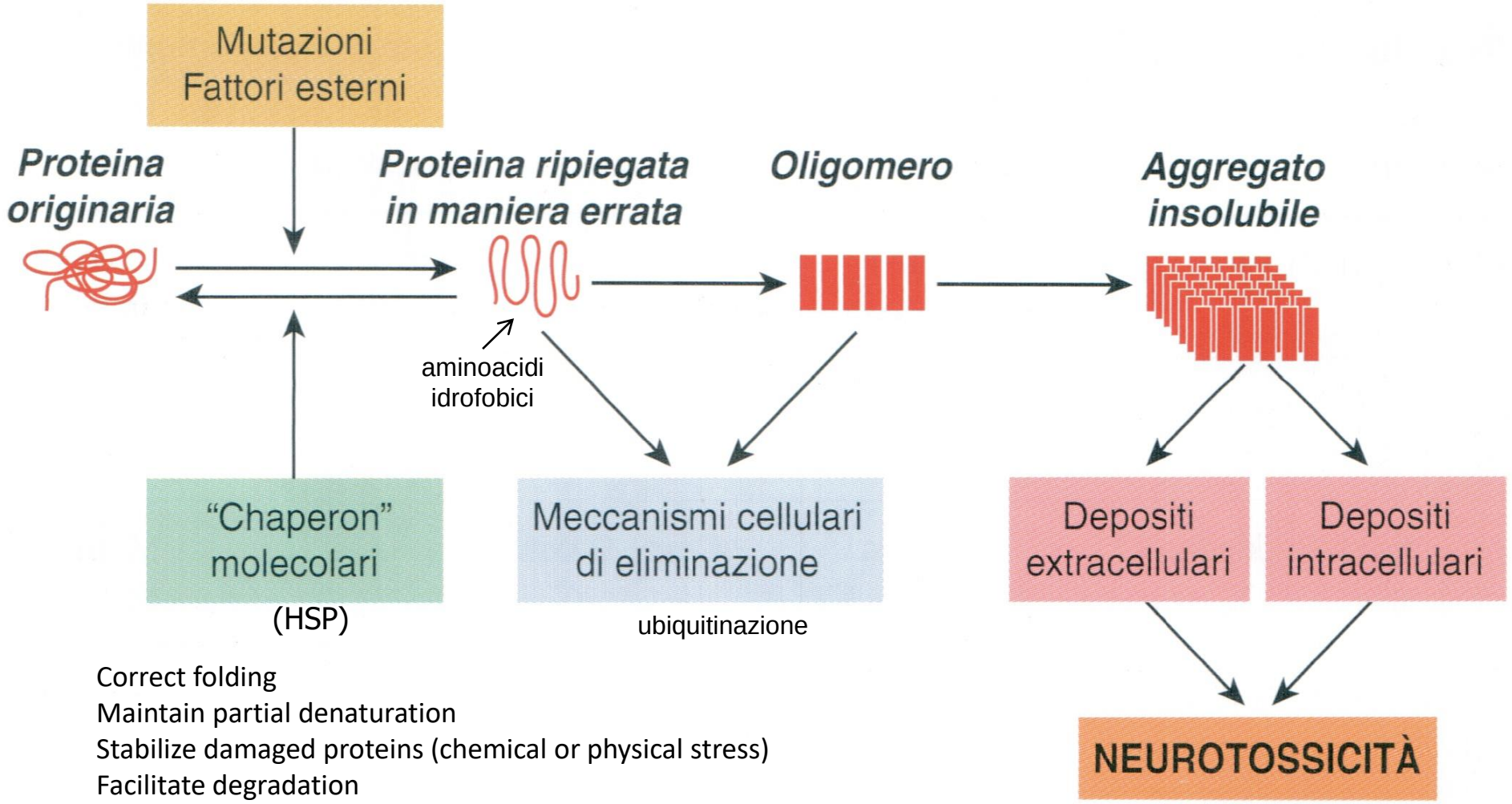
- **Alzheimer's disease (AD)**
- **Parkinson's disease (PD)**
- **Huntington's disease (HD)**
- **Amyotrophic Lateral Sclerosis (ALS)**
- **Multiple Sclerosis (MS)**

  - **Common features:**
    - **Progressive & irreversible loss of neurons**
    - **Characterized by protein aggregation**
    - **Selective vulnerability of neuronal populations**
    - **Role of genetics, environment**
    - **Current therapies address symptoms but do not affect disease processes**

Proteinopathies
Accumulation of cellular proteins as aggregates



“Misfolding” of proteins

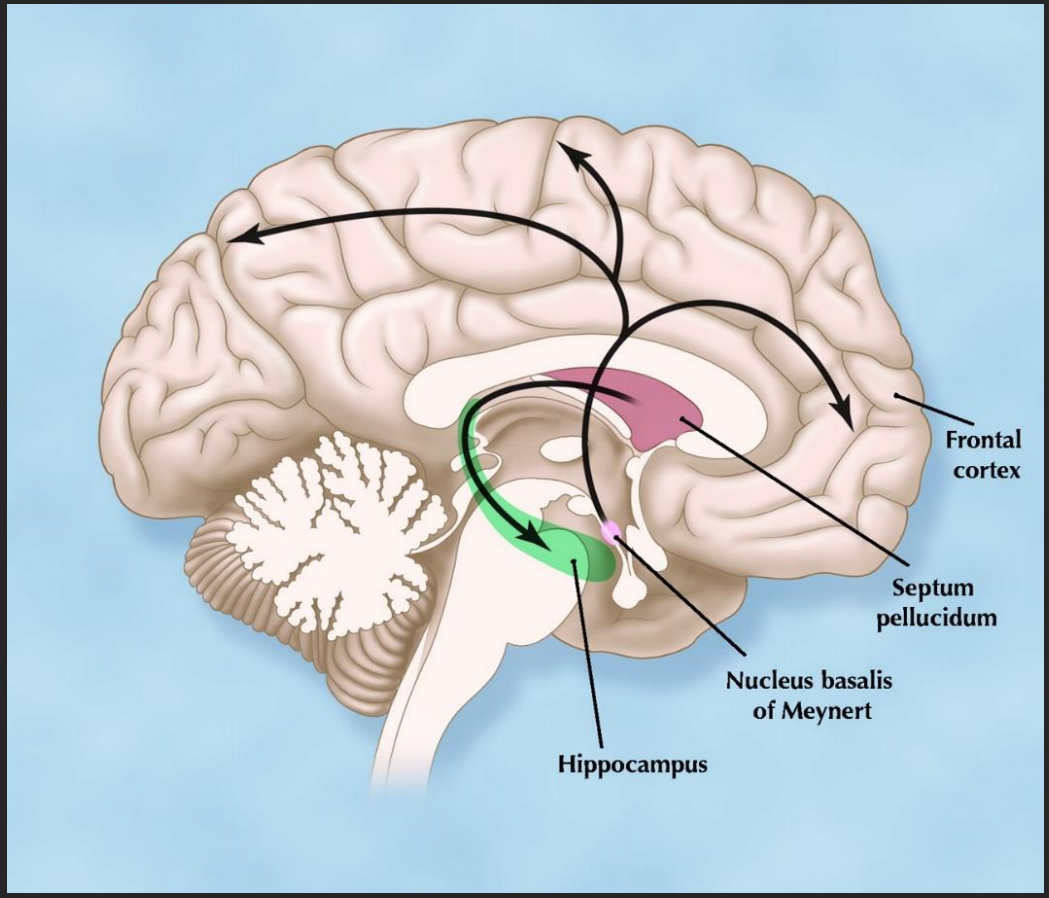


Correct folding
Maintain partial denaturation
Stabilize damaged proteins (chemical or physical stress)
Facilitate degradation

Selective Vulnerabilty

ALZHEIMER:

neuronal degeneration of the nucleus basalis of Maynert, of the hippocampus and of the cortex (non-uniform neuronal loss in various brain structures)



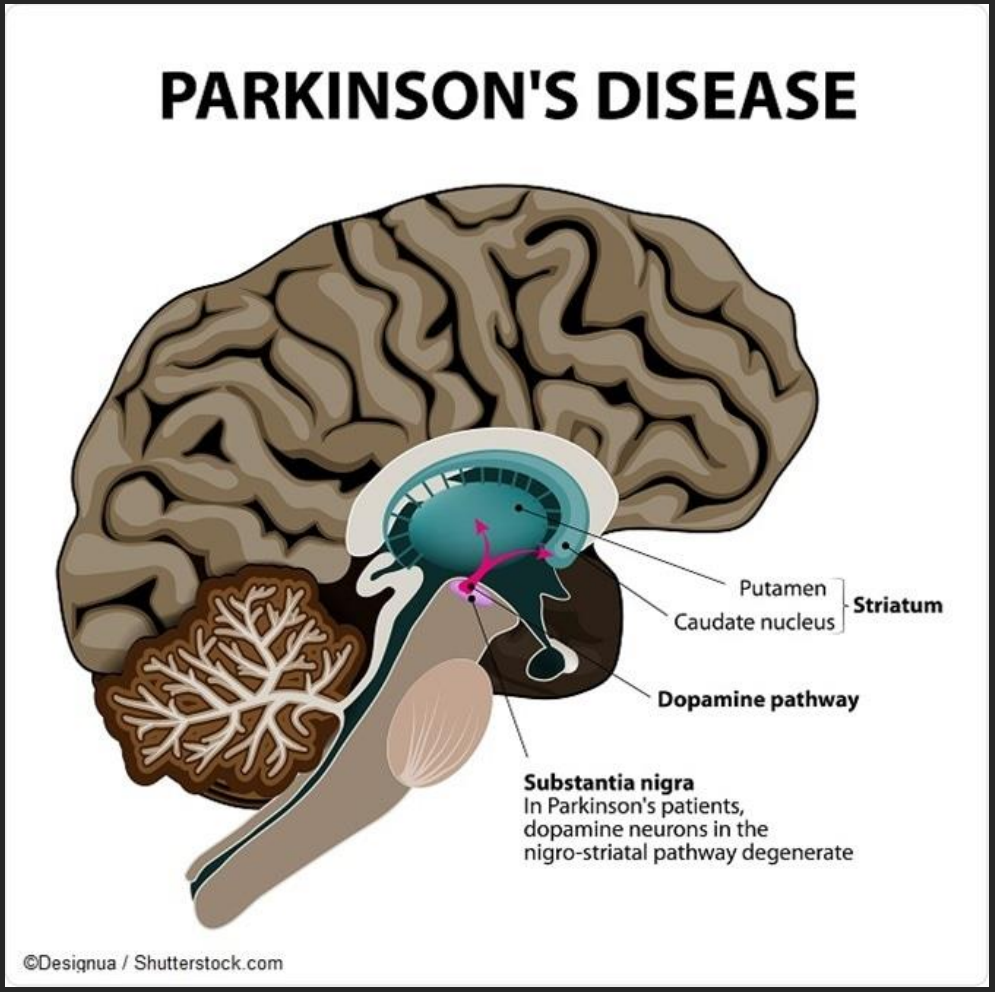
Selective Vulnerabilty

PARKINSON:

degeneration of

dopaminergic neurons of the

substantia nigra



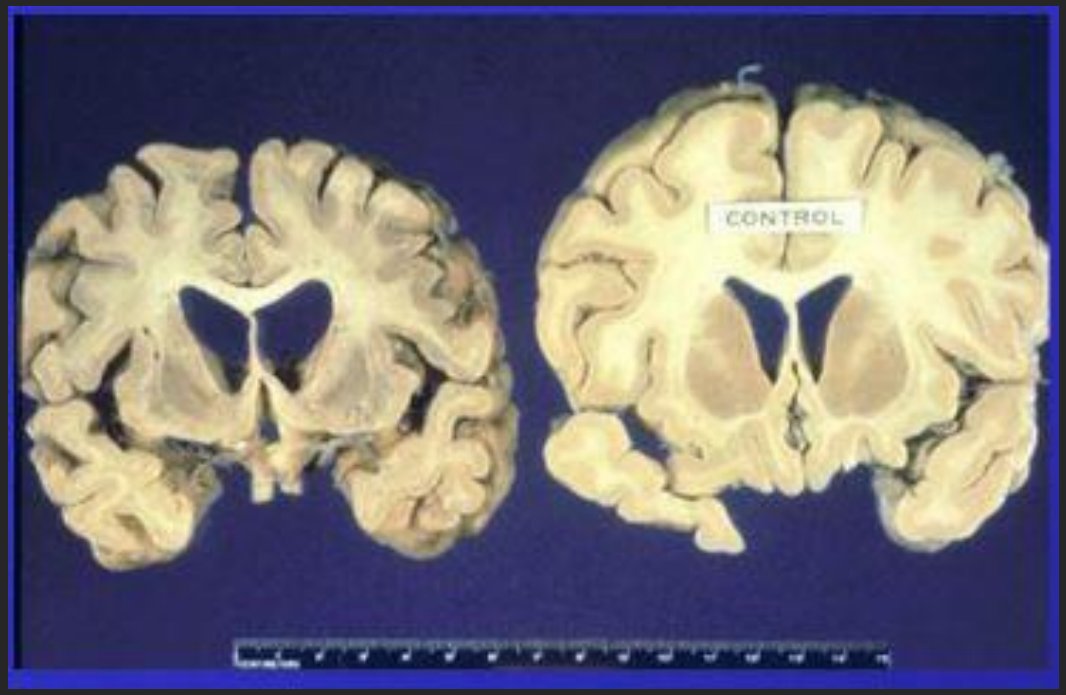
Selective Vulnerability

HUNTINGTON Disease:

degeneration of

Caudate-Putamen

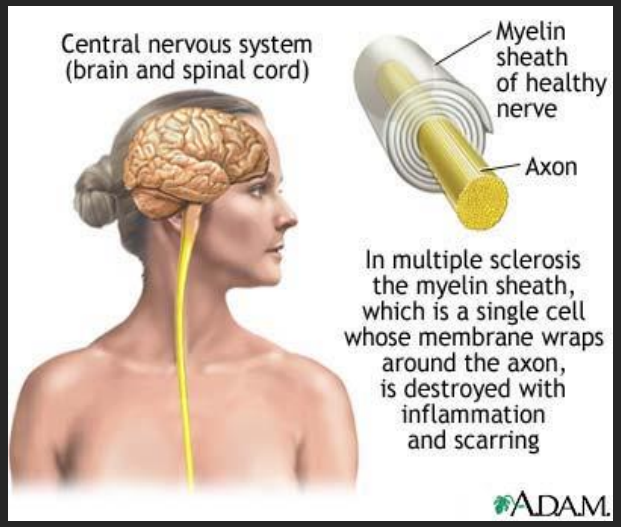
neurons

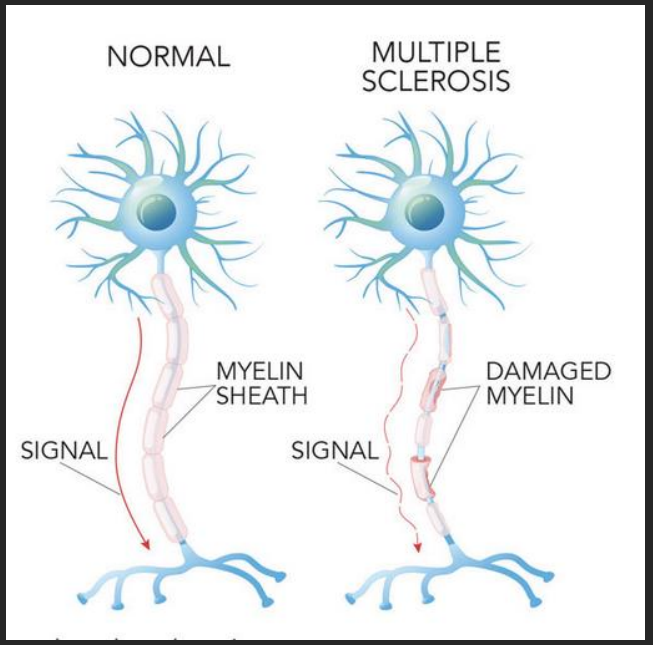


Selective Vulnerability

Multiple Sclerosis (MS)

Chronic autoimmune disease characterized by demyelination of neurons





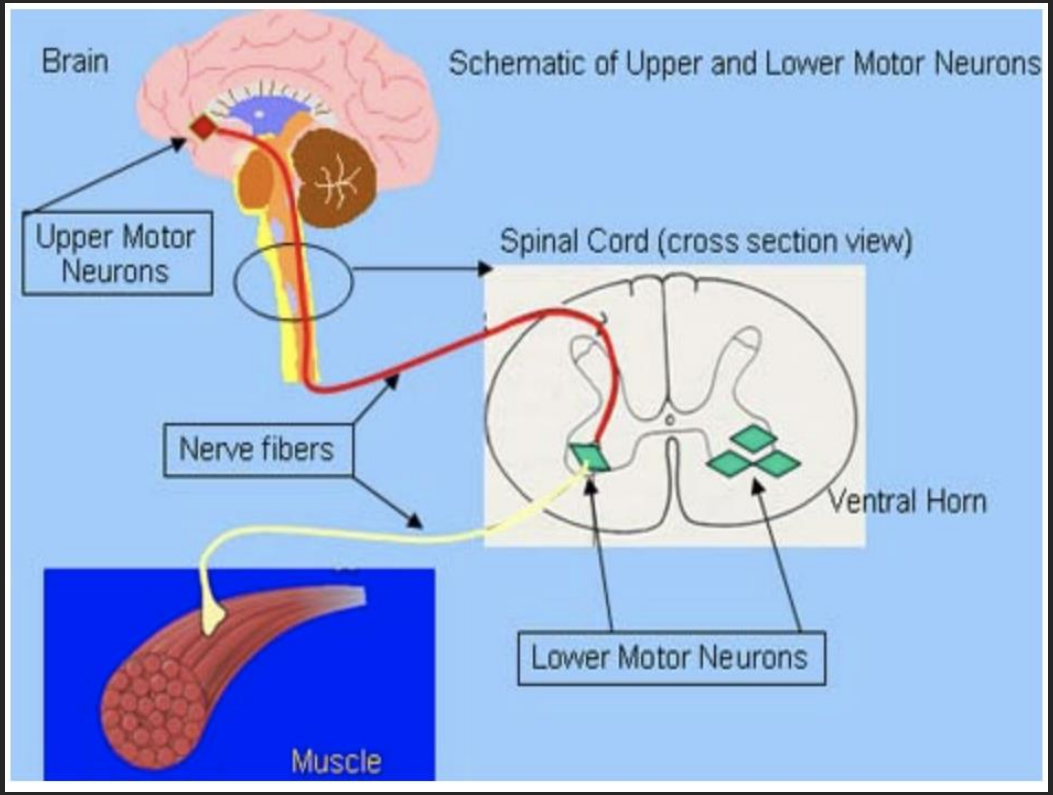
https://www.beaumont.org/conditions/multiple-sclerosis

Selective Vulnerability

Amyotrophic Lateral Sclerosis (ALS)

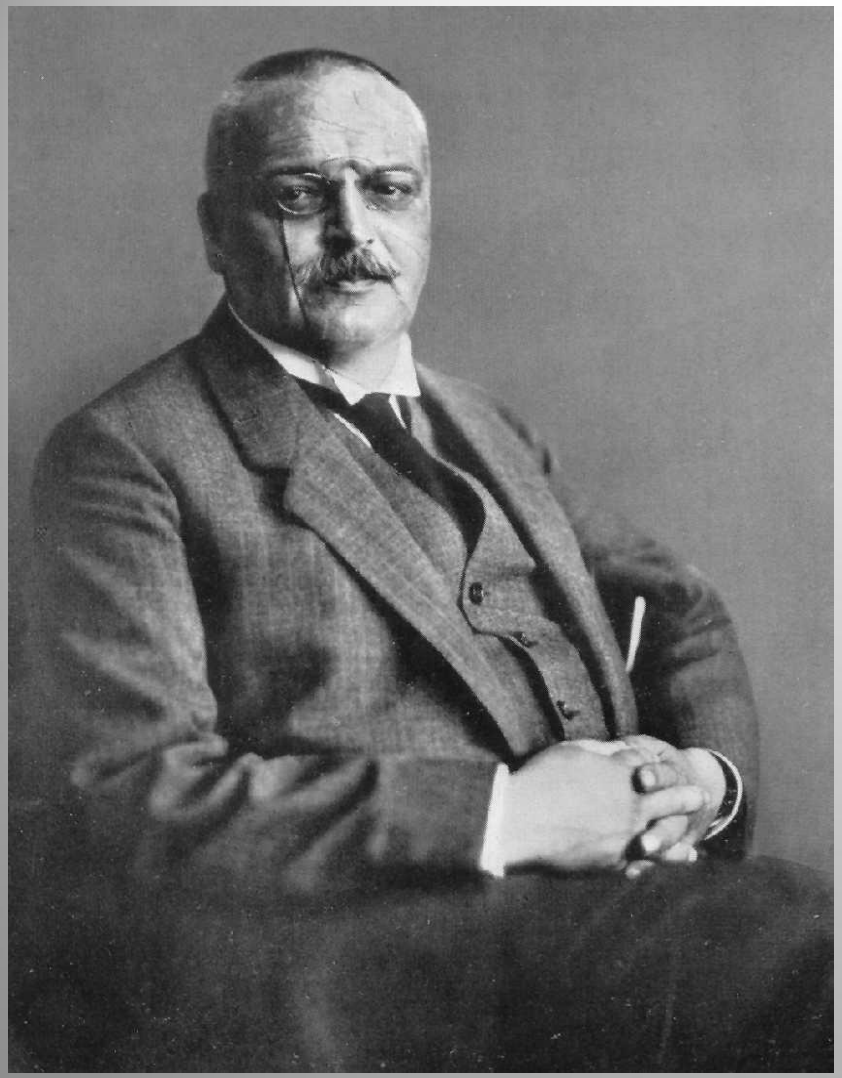
Degeneration of upper motor neurons (brain) & lower motor neurons (spinal cord)

Also know as: Lou Gehrig's disease & Charcot's disease



alsa.org/site/PageServer?pagename=ALSA_Disease_Process_ALS

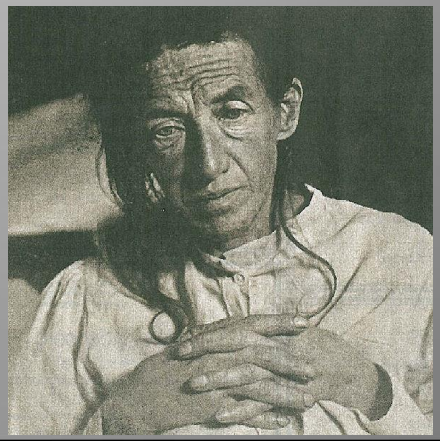
Alzheimer Disease



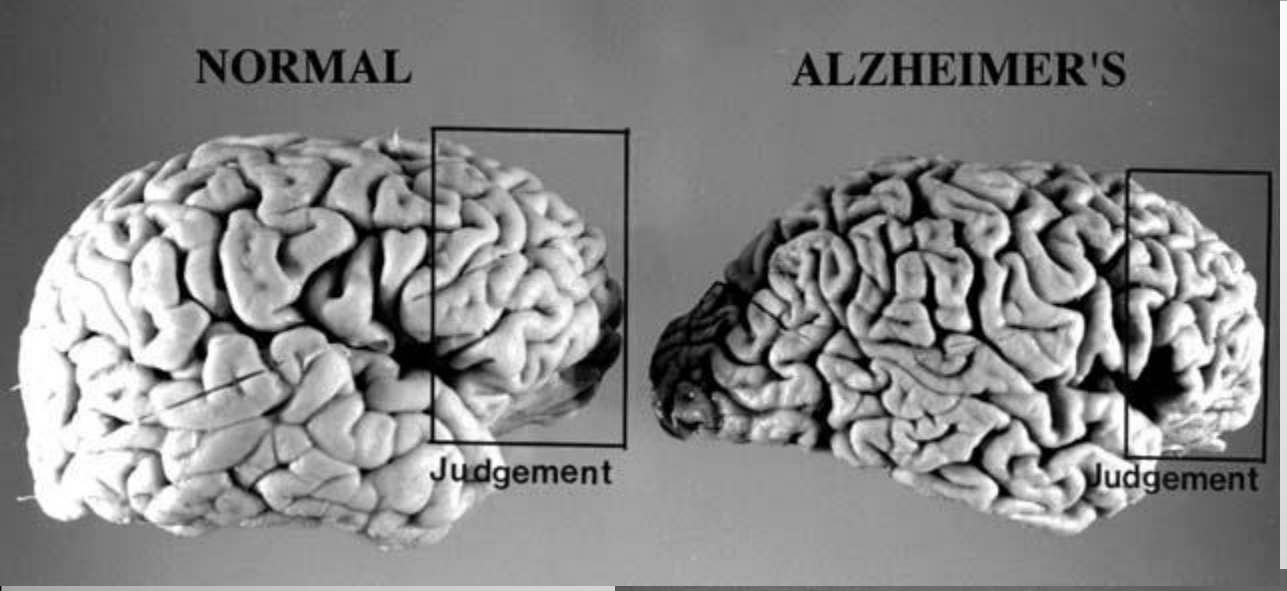
Alois Alzheimer

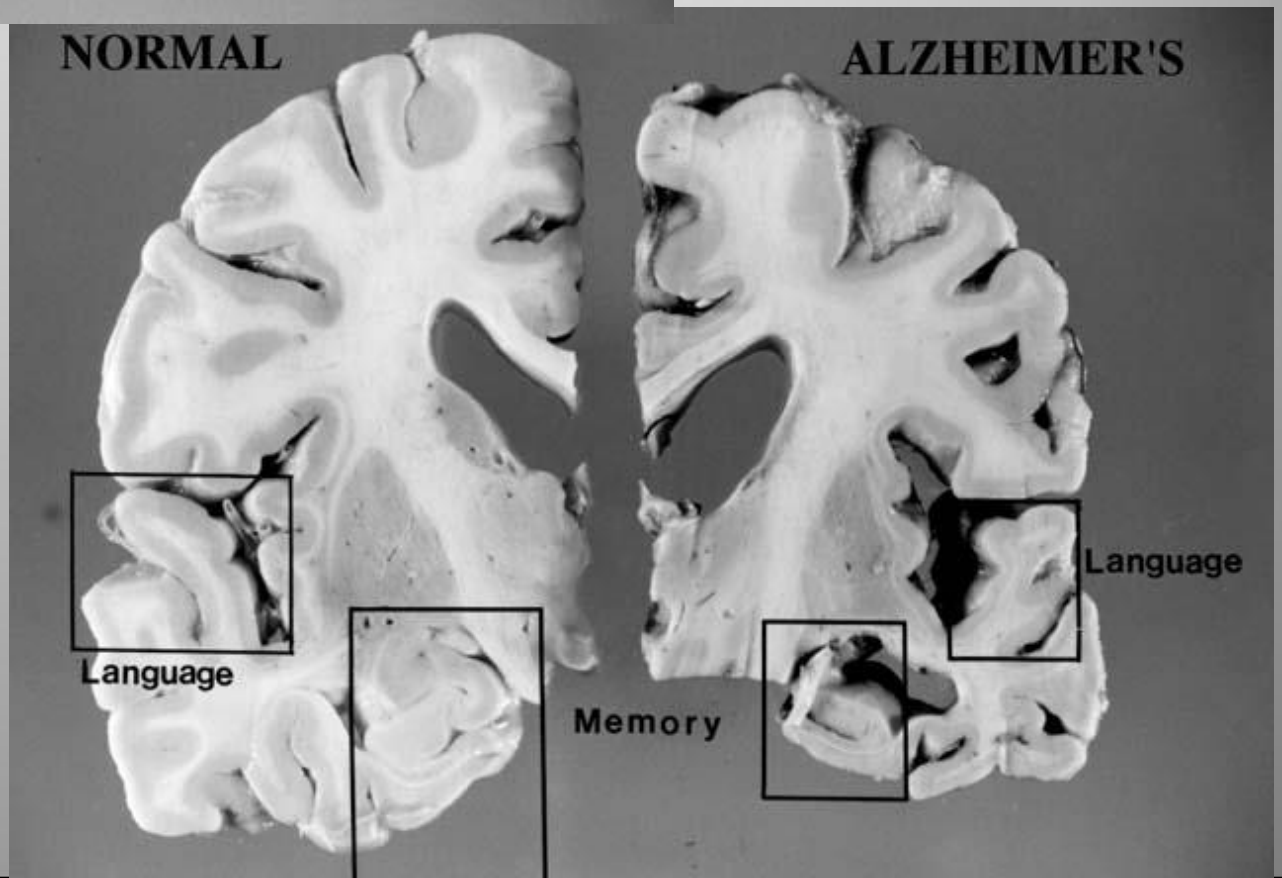
Birth:	Jun. 14, 1864
Death:	Dec. 19, 1915

3 November 1906 would be the first time the pathology and the clinical symptoms of presenile dementia would be presented together Franz Nissl



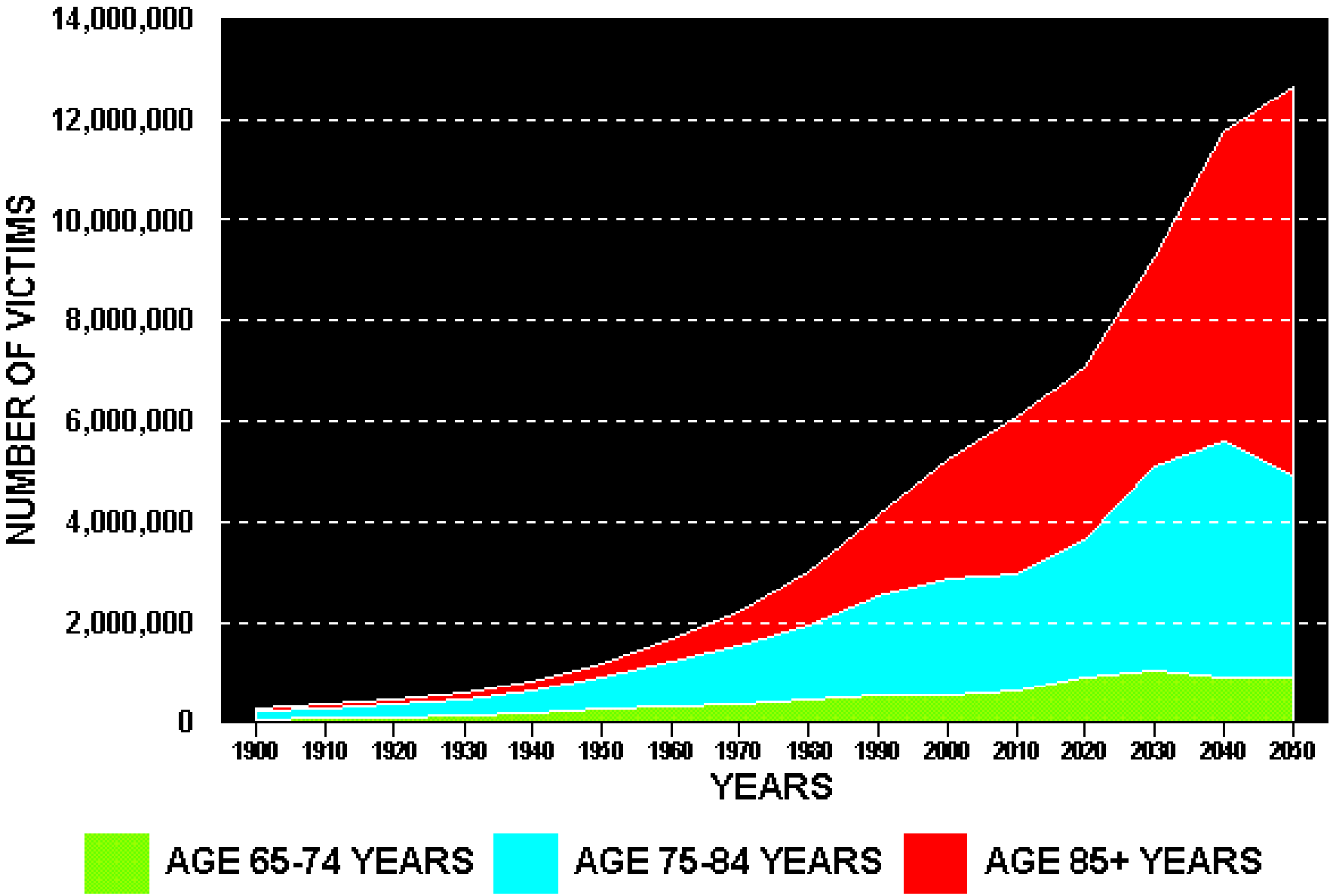
Mrs. Auguste Deter


NORMAL
ALZHEIMER'S
Judgement
Judgement


NORMAL
ALZHEIMER'S
Language
Language
Memory

PREVALENCE OF ALZHEIMER'S DISEASE

(BY DECADES IN U.S.A. FROM 1900-2050)



Alzheimer's Disease Symptoms

Cognitive

Memory loss
Absence of logical thoughts
Confusion
Disorientation

Behavioral

Agitation / anxiety
Delusions, hallucinations
Depression
Insomnia
Poor attention

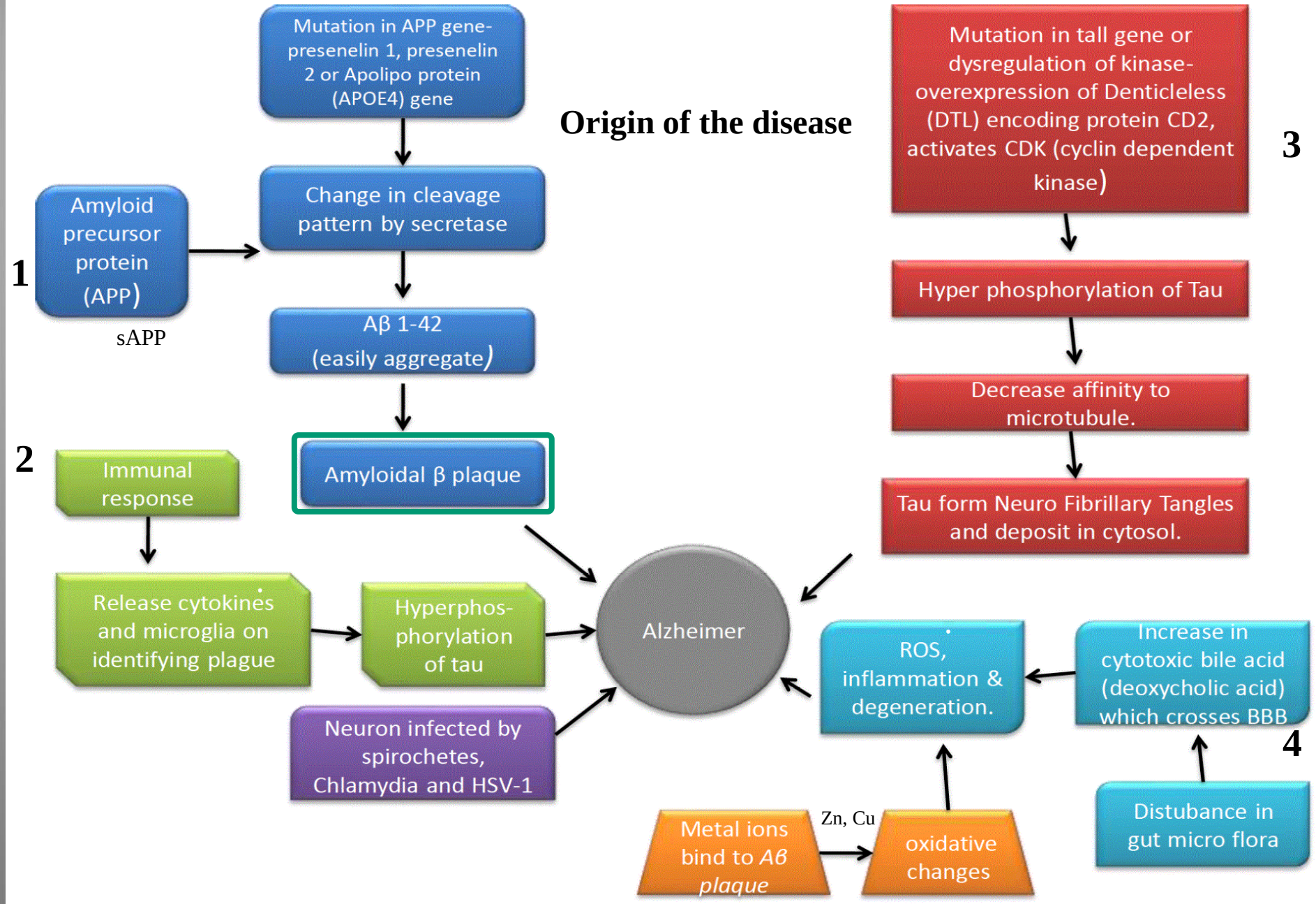
GRADUAL ONSET AND CONTINUING PROGRESS

Mini-Mental State Exam (MMSE)

Exam consists of questions referring to seven different cognitive areas:
- orientation in time
- orientation in space
- word registration
- attention and calculation
- recalling
- language
- constructive praxia (finalized gestures)

Scoring
30 normal
Slight 21-26
Moderate 10-20
Moderate-Severe 10-14
Severe < 10

Origin of Alzheimer Disease


Origin of the disease
1
Amyloid precursor protein (APP)
sAPP
Mutation in APP gene- presenelin 1, presenelin 2 or Apolipo protein (APOE4) gene
Change in cleavage pattern by secretase
Aβ 1-42 (easily aggregate)
Amyloidal β plaque
2
Immunal response
Release cytokines and microglia on identifying plague
Hyperphos- phorylation of tau
Neuron infected by spirochetes, Chlamydia and HSV-1
Alzheimer
3
Mutation in tall gene or dysregulation of kinase- overexpression of Denticleless (DTL) encoding protein CD2, activates CDK (cyclin dependent kinase)
Hyper phosphorylation of Tau
Decrease affinity to microtubule.
Tau form Neuro Fibrillary Tangles and deposit in cytosol.
ROS, inflammation & degeneration.
Increase in cytotoxic bile acid (deoxycholic acid) which crosses BBB
4
Distubance in gut micro flora
Metal ions bind to Aβ plaque
Zn, Cu
oxidative changes

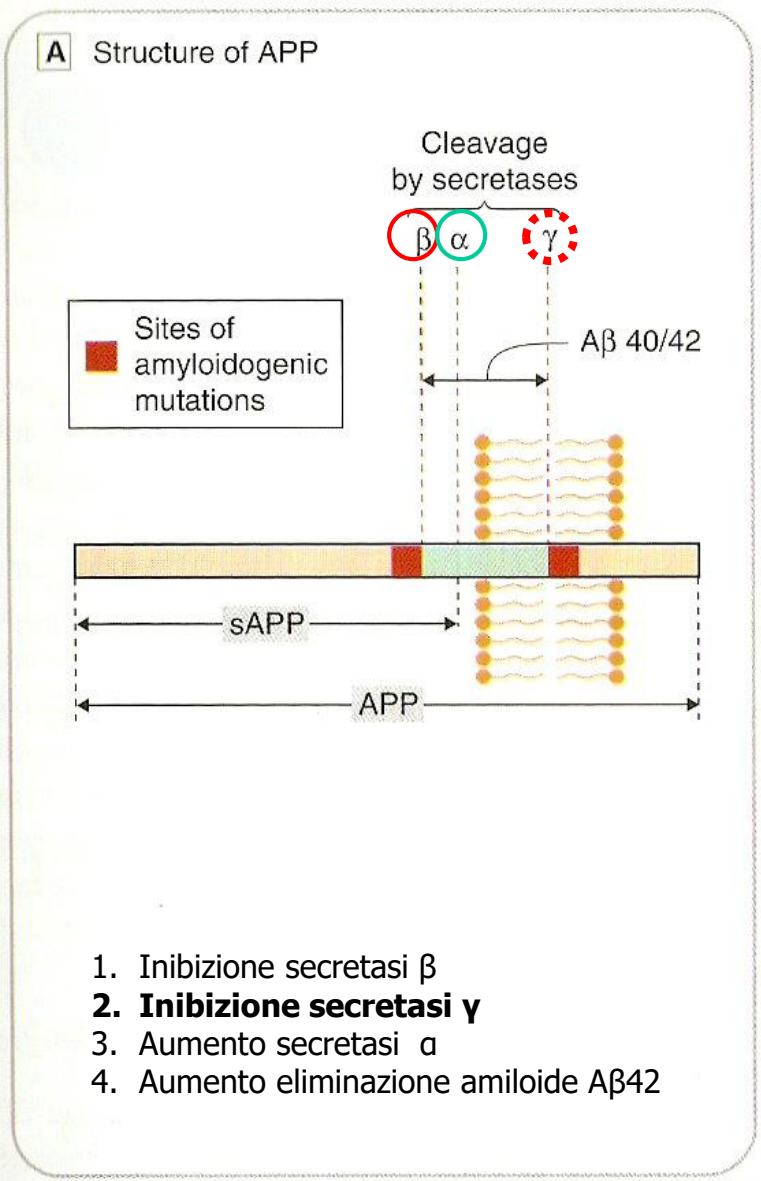
Alzheimer's Disease Pathology

Accumulation of protein aggregates outside & inside neurons

Amyloid plaques (senile) located outside neurons; composed of amyloid beta protein (A-beta) derived from processing **amyloid precursor protein (APP)** by secretases; gene chromosome 21

Neurofibrulary tangles located inside neurons; composed of **Tau protein,** which normally interacts with microtubules; gene chromosome 17

Alzheimer Disease Pathology



1. Inibizione secretasi β
2. **Inibizione secretasi γ**
3. Aumento secretasi α
4. Aumento eliminazione amiloide Aβ42

Importance of microglia and astroglia

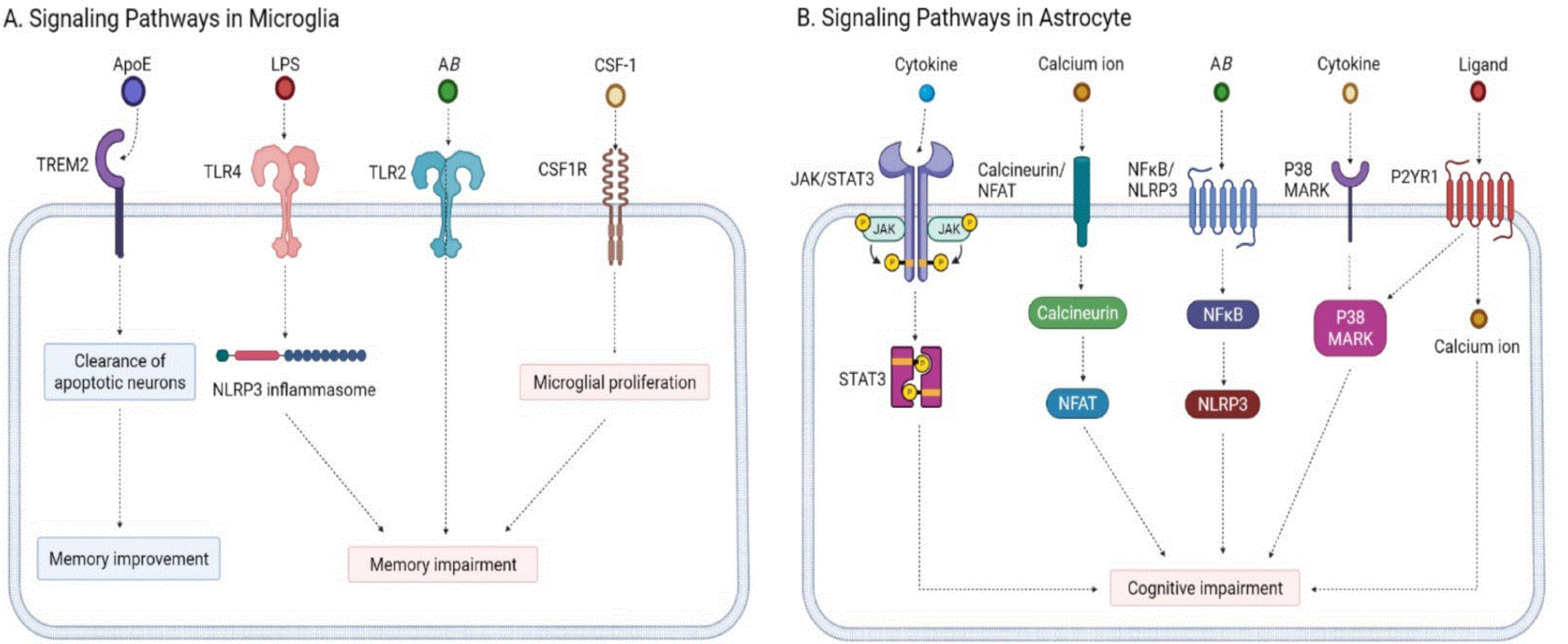
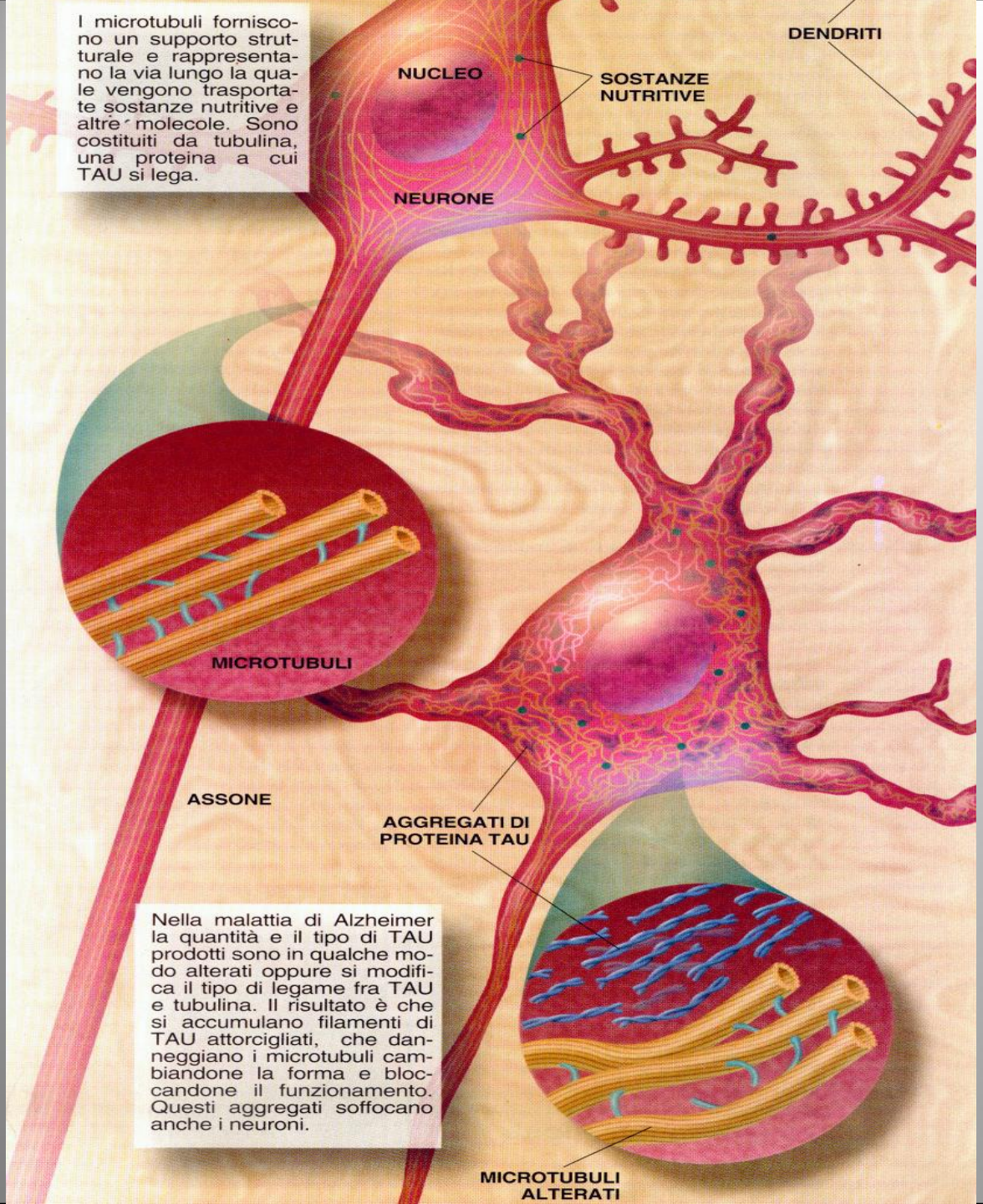
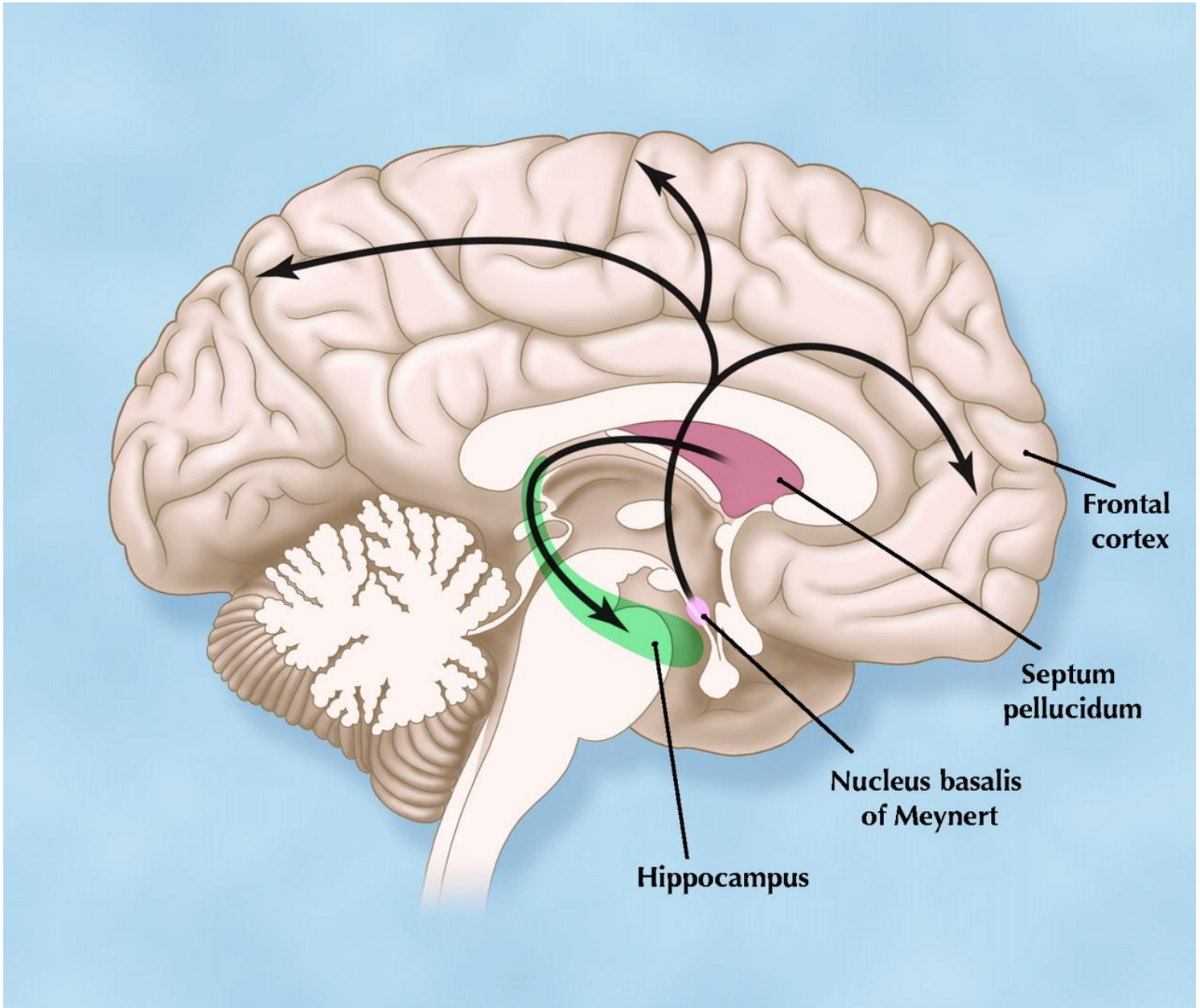


Figure 1. Signaling pathways of microglia modulators and astrocyte modulators. (**A**) Signaling pathways in microglia; (**B**) signaling pathways in astrocytes. Created with BioRender.com. * TREM2—triggering the receptor expressed on myeloid cells 2, TLR—Toll-like receptor, CSF1R—colony-stimulating factor-1 receptor, JAK—Janus kinase, STAT3—signal transducer and activator of transcription 3, NFAT—nuclear factor of activated T cells, NFκB—nuclear factor-kB, NLRP3—nod-like receptor family pyrin domain containing 3, MAPK—mitogen-activated protein kinase, P2Y1R—P2Y1 purinoreceptor.

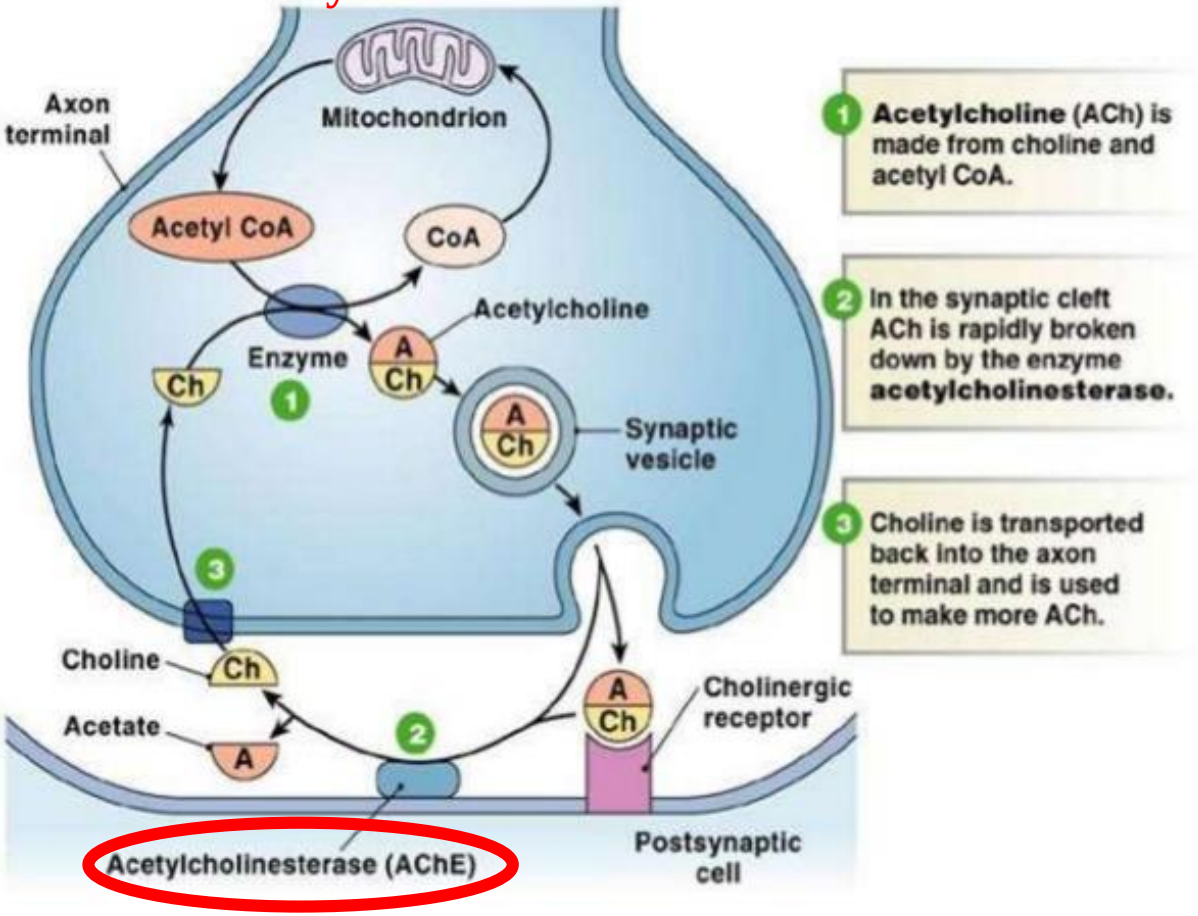

I microtubuli forniscono un supporto strutturale e rappresentano la via lungo la quale vengono trasportate sostanze nutritive e altre molecole. Sono costituiti da tubulina, una proteina a cui TAU si lega.
NUCLEO
SOSTANZE NUTRITIVE
DENDRITI
NEURONE
MICROTUBULI
ASSONE
AGGREGATI DI PROTEINA TAU
Nella malattia di Alzheimer la quantità e il tipo di TAU prodotti sono in qualche modo alterati oppure si modifica il tipo di legame fra TAU e tubulina. Il risultato è che si accumulano filamenti di TAU attorcigliati, che danneggiano i microtubuli cambiandone la forma e bloccandone il funzionamento. Questi aggregati soffocano anche i neuroni.
MICROTUBULI ALTERATI

TAU Protein

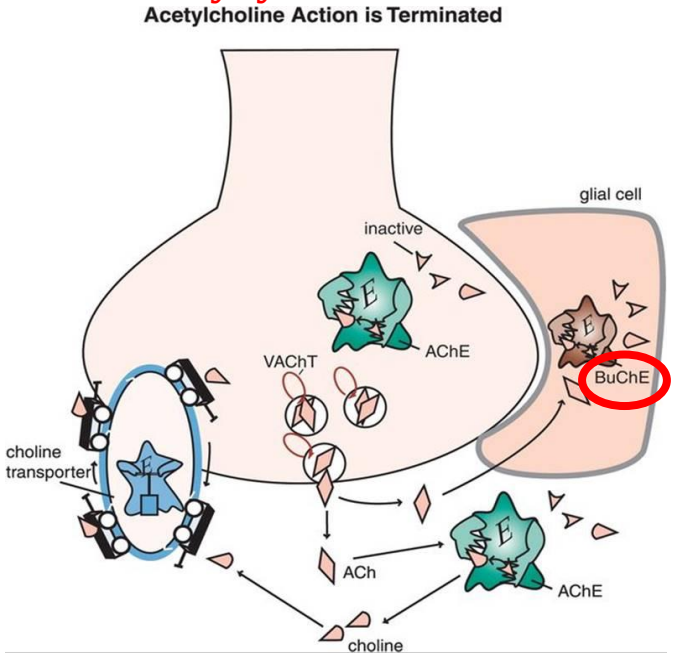
Alzheimer Disease and Acetylcholine



Acetylcholinesterase



Butyrylcholinesterase



It increases with the progress of the disease, while it is low in physiological conditions

Cholinesterase enzymes carry out a peptidase action of APP, contributing to the formation of plaques

THERAPY

SYMPTOMATIC therapy

- **SPECIFIC DRUGS** (ACE inhibitors,NMDA antagonists))
- **ASPECIFIC DRUGS**

-NOOTROPICS (Piracetam, Ginko)

-ANTIPSYCHOTICS

Lack of drugs that lead to regression of the disease

B secretase inhibition
Y secretase inhibition
Increased α-secretase
Increased amyloid elimination Aβ42

Memantine

- NMDA non-competitive antagonist

Side effects: dizziness, vomiting, increased blood pressure, epilepsy

Donepezil

- Selective inhibitor of ACE in the CNS (does not act on butyrylcholinesterase)
- Long half-life, Improvement of cognitive symptoms

Low side effects (ulcer, disturbance conduction Atrio-Ventricular, respiratory disturbance)

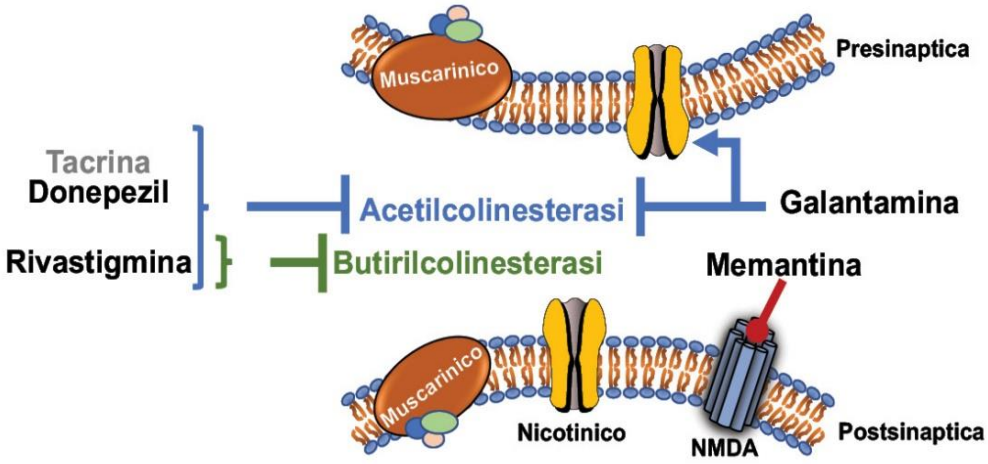
RIVASTIGMINE AND GALANTAMINE

They have similar effects to donepezil (shorter duration of action)

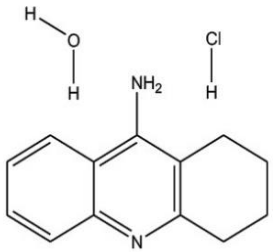
Side effects: vomiting, diarrhea, ulcer

~~**Tacrine**~~

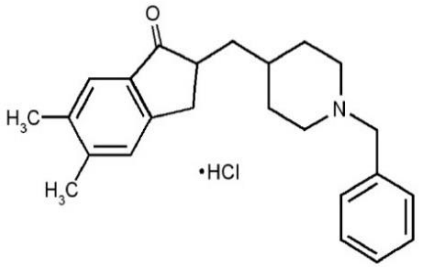
~~**- Side effects: abdominal cramps, nausea, anorexia, increased transaminases, hepatotoxicity, short duration of action**~~



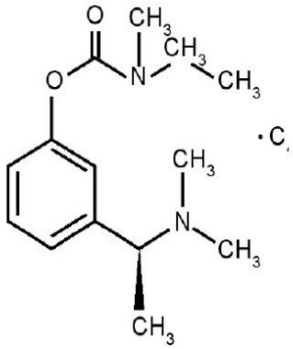
1993
Tacrine
(Cognex®)



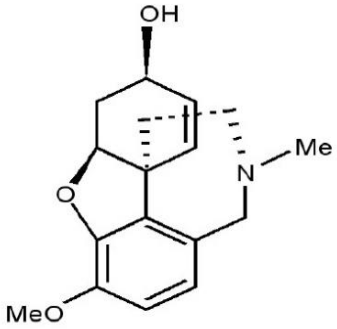
1997
Donepezil
(Aricet; Memac)



2000
Rivastigmine
(Exelon®)



2001
Galantamine
(Reminyl®)



2004
Memantina
(*Ebixa*)

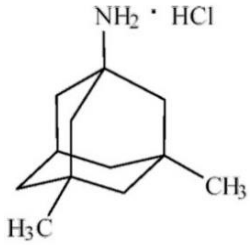


TABLE 3

Adverse effects of cognitive enhancers: Percent of patients affected

	Cholinesterase inhibitors				NMDA receptor antagonist
	Donepezil	Galantamine	Rivastigmine	Rivastigmine transdermal	Memantine
Nausea	3%–19%[a]	21%	17%–47%	2%–4%	Not available
Diarrhea	5%–15%[a]	7%	5%–19%	≤ 7%	5%
Constipation					3%–5%
Anorexia	2%–8%	7% (decreased appetite)	≥ 17% 3%–26% (weight loss)	≤ 3%	< 1% 3% (weight gain) (extended-release formulation)
Vomiting	3%–9%[a]	11%	13%–31%	3%–9%	2%–3%
Insomnia	2%–14%	Not available	1%–9%	Not available	Not available
Headache	3%–10%	7%	4%–17%	≤ 4%	6%
Dizziness	2%–8%	8%	6%–21%	≤ 6%	5%–7%
Fatigue	1%–8%	4%	4%–9%	2%–4%	2%
Syncope	2%	1%	3% (falling) 6%–12%	Not available	Not available
Bradycardia	≥ 1%	1%	< 1%	< 1%	< 1%
Infection	11%	< 1%	1%–10% (urinary tract infections)	Not available	4% (influenza)

[a]Dose-related.
NMDA = *N*-methyl-D-aspartate

TABLE 2

Alzheimer disease: Severity, associated symptoms, and recommended treatment

Dementia category	Global Deterioration Scale (stages 1–7)	Medications
Not demented	**1** No cognitive impairment **2** Very mild decline: age-associated cognitive impairment **3** Mild cognitive impairment, minor neurocognitive decline	No indication for cognitive enhancers
Mild dementia	**4** Decreased knowledge of current and recent events Decreased ability to travel, handle finances, and manage basic activities of daily living	Cholinesterase inhibitors
Moderate dementia	**5** Unable to recall a major relevant aspect of their current life, an address or telephone number of many years, or the names of close family members Basic activities of daily living begin to be impaired	Cholinesterase inhibitors with or without an NMDA receptor antagonist
Severe dementia	**6** Occasionally forgets the name of the spouse or caregiver on whom he or she is entirely dependent Unaware of all recent events and experiences in their lives Most basic activities of daily living impaired	Cholinesterase inhibitor (donepezil) with or without an NMDA receptor antagonist
Advanced dementia	**7** Cannot speak or walk, has incontinence and difficulty swallowing	No randomized controlled trials in stage 7

NMDA = *N*-methyl-D-aspartate

https://consultqd.clevelandclinic.org/alzheimer-dementia-starting-stopping-drug-therapy/

Directions

- Do not use AchE inhibitors in combination (memantine only)
- Titration of the drug in the patient
- AchE inhibitors in mild and moderate forms
- After 3 months it is continued only if stable or improved patient

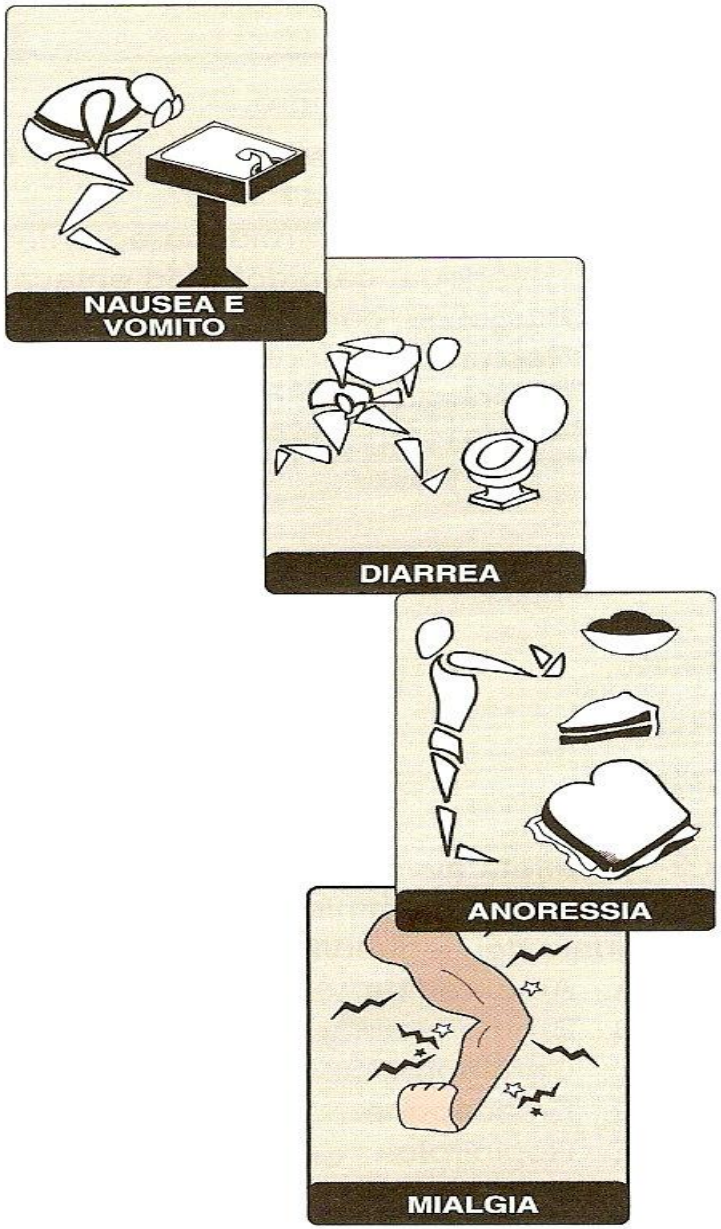
OTHER DRUGS

Anxiolytics, Antidepressants, Antipsychotics (symptoms)

DIHYROERGOTAMIN, IDERGINE : Brain vasodilator

PIRACETAM, ANIRACETAM
Nootropics increase glutamate release (little effective in AD)

Side Effects of dell'acetylcholinesterase (AchE) inhibitors



CYP 3A4, 2D6

Inhibitors:
Itraconazole
Erythromycin
Fluoxetine

Inductors:
Rifampicin
Phenytoin
Carbamazepine
Alcohol

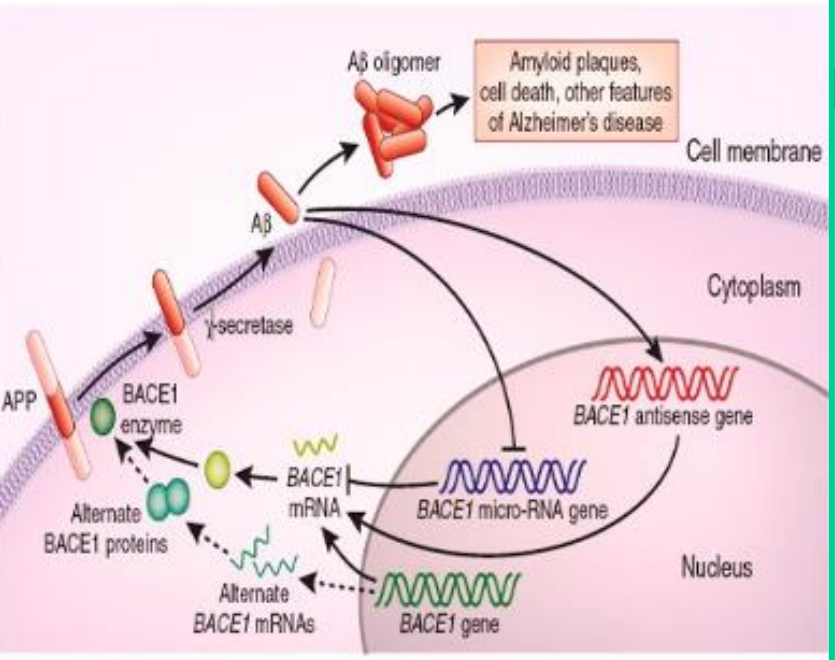
Fatigue
Insomnia

New therapies for Alzheimer Disease

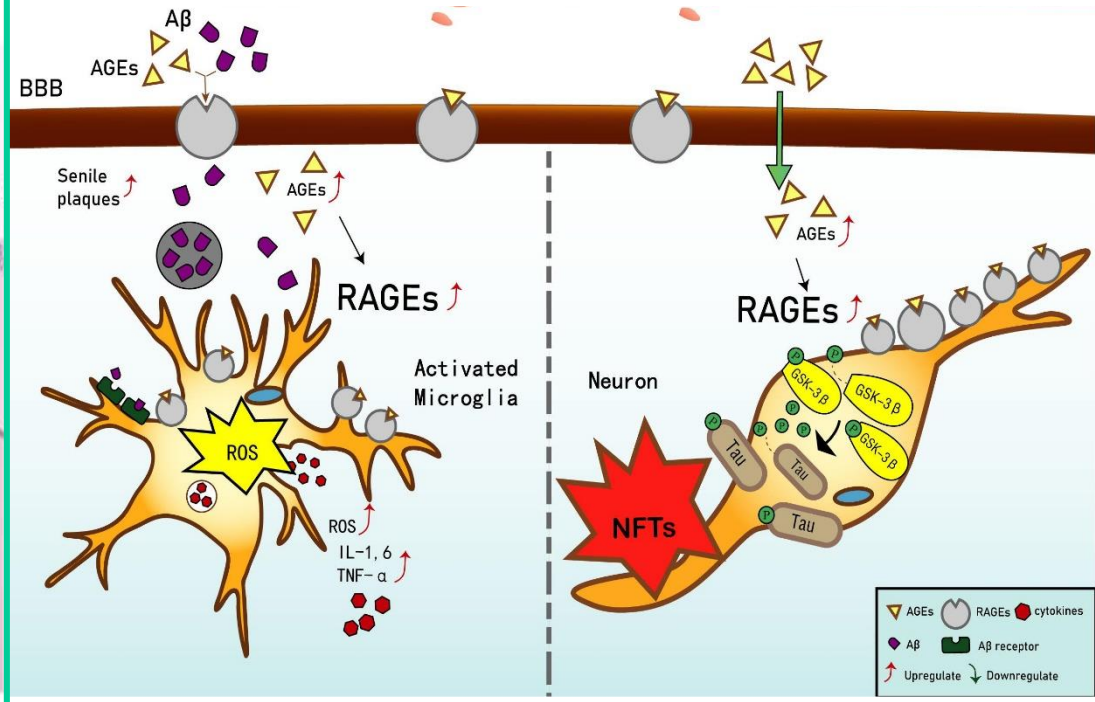

Blood and Urine
MCI Biomarkers
CSF Proteins
Brain Lipids Biomarkers
Genetic Materials
Biomarkers
Peptidomimetics
Immuno Therapy
FDA approved medicine
Gene Therapy
Metal chelators
Prebiotics, probiotics & exercise.
ALZHEIMER
Strategies In Treatment
Strategies In Early Detection
Brain Imaging
Artificial Intelligence
eg. NIR
Theranostics

*

Beta-site APP cleaving enzyme 1 (BACE1)



Receptor of advanced glycation end products (RAGE)



Neurofibrillary tangles (NFTs)
Glycogen Synthase Kinase (GSK)
Beta Amyloid Protein (AB)

Peroxisome Proliferator-Activated Receptors (PPARs)

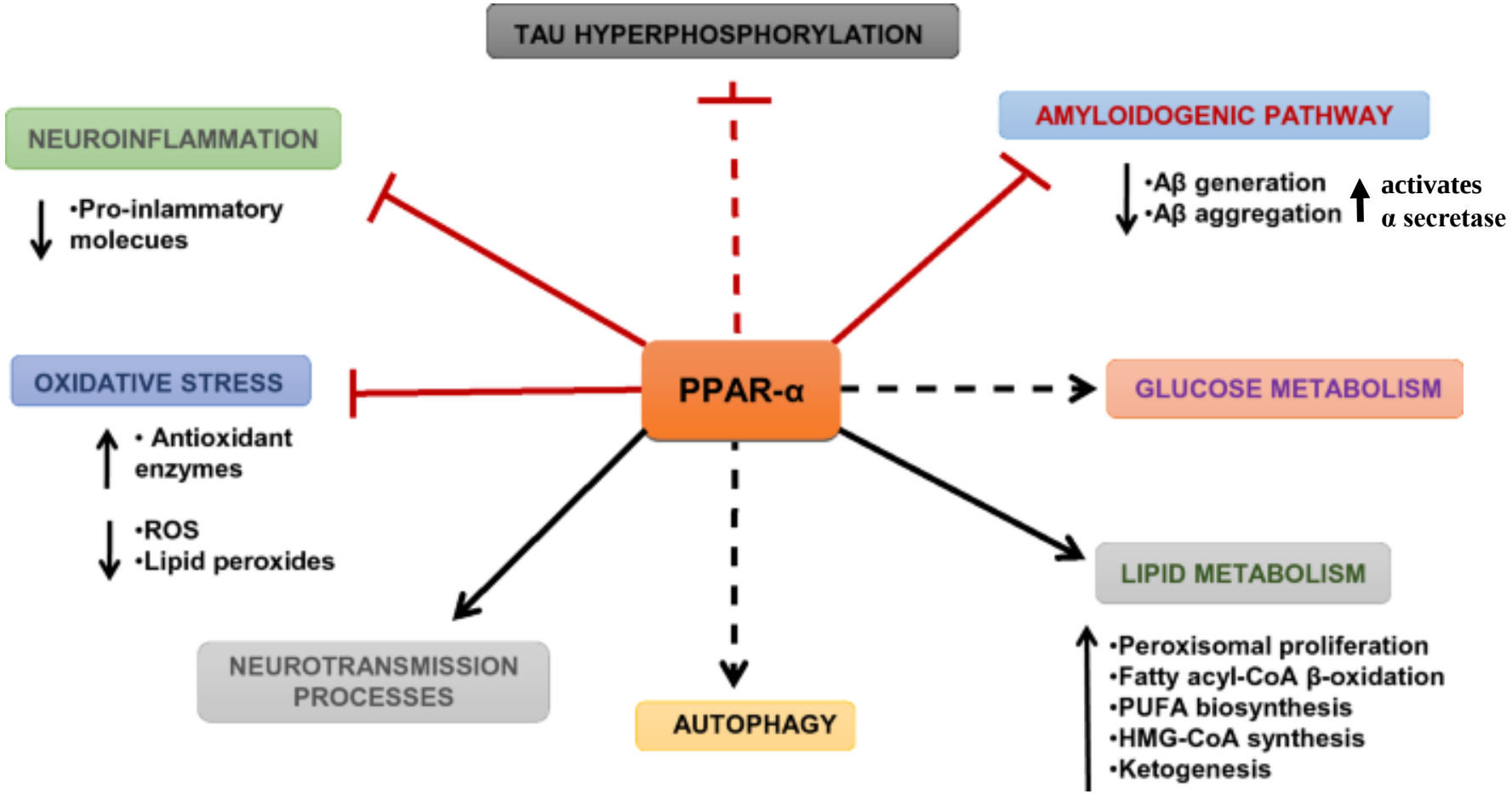


Table 1. Drugs developed for the treatment of Alzheimer's disease

Name of the Drug	Company	Mechanism of Action	Clinical Trial	Reason for Failure
Verubecestat	Merck	β-site amyloid precursor protein-cleaving enzyme 1 (BACE 1) inhibitors	EPOCH trial APECS trial	No effect on slowing the progression of AD
Lanabecestat	Astra Zeneca & Eli Lilly	BACE 1 inhibitors	AMARANTH and DAYBREAK-ALZ	Failure of interim futility analysis
Atabecestat	Janssen Eli Lilly	BACE 1 inhibitors	EARLY [illegible]	Liver toxicity nitive decline
Azeliragon	vTv Therapeutics	Receptor for Advanced Glycation End products (RAGE) inhibitor	STEADFAST (Phase III)	Lack of efficacy
Pioglitazone	Takeda and Zinfandel Pharmaceuticals	Peroxisome Proliferator-Activated Receptor γ (PPAR-γ)	-	-
Idalopirdine	Lundbeck & Otsuka	5HT6 antagonist	STARSHINE, STARBEAM, STARBRIGHT (Phase III)	Did not improve cognition

Immunotherapy
Active or Passive Immunization

- Active immunization: *Aβ-42* can stimulate B-cells, T-cells and microglia for immune response

- Passive immunization: administration of monoclonal antibodies (mAb)

Name	Mechanism	Phase of Clinical Trial
ACI-24	Cause production of antibodies against Aβ without activating inflammatory cells.	Phase 1
ACI-35	Liposome based vaccine which generates antibodies against phosphorylated tau.	Phase 1
ABvac40	Targets C-terminus of Aβ40	Phase 2
AADvac-1	Consist of Peptide (KDNIKHVPGGGS) which generate antibodies against tau.	Phase 3
CAD106	Virus based active vaccine which target Aβ without activating T cells.	Phase 2
LuAF20513 (engineered mixed peptide antigen)	Generate anti Aβ antibodies without microglial activation.	Phase 1
DNA based vaccine	Translation of Aβ based DNA leads to generation of antibodies.	Early stage of development
Passive Immunotherapeutic		
Drug	**Mechanism**	**Phase of Clinical Trials**
Aducanumab	Monoclonal antibody against Aβ	Phase 3
Crenezumab	Humanised monoclonal antibody which mainly identifies polymorphic form of Aβ	Phase 3
Gantenerumab	Binds to Aβ and induce phagocytosis by activating microglia.	Phase 3
BAN2401	Preferentially binds to soluble photofibrils of Aβ	Phase 2
Bapineuzumab (Humanised form of murine monoclonal antibody)	Target N- terminal region of Aβ	Failed in clinical trials
Solanczumab	Targets monomeric and non-fibrillary form of Aβ peptides	Phase 3
BIIB092	Targets N terminal fragment of tau	Phase 2
C2N 8E12	Targets extracellular tau aggregates.	Phase 2