BIOENG-480
NEUROSCIENCE 1.
MOLECULES AND NEURODEGENERATION

FALL SEMESTER 2018-2019

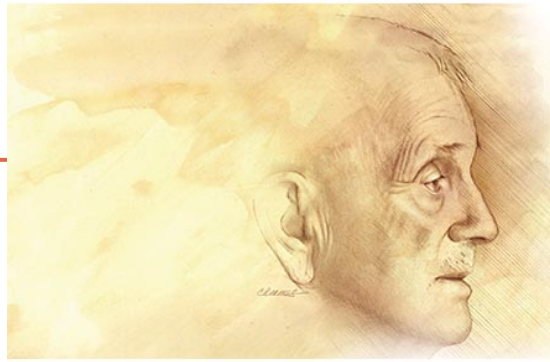
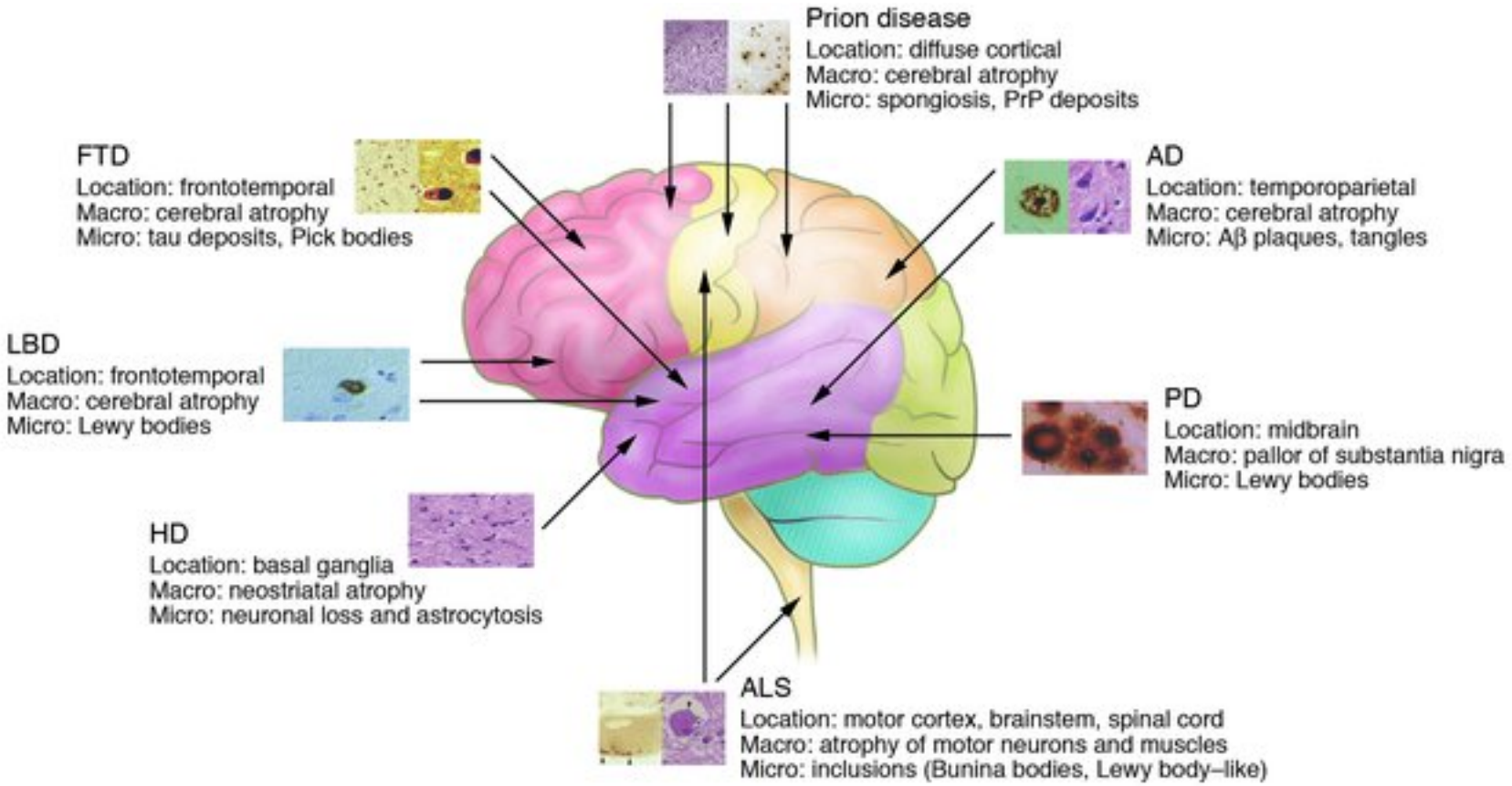


Illustration courtesy of the Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging

ALZHEIMER'S DISEASE
FROM GENES TO MECHANISMS TO THERAPIES

H. LASHUEL

What do these diseases have in common?



Lars Bertram, Rudolph E. Tanzi, *J Clin Invest.* 2005;115(6):1449-1457. doi:10.1172/JCI24761.

Alzheimer's Disease – Overview

1 Test your knowledge about Alzheimer's disease

2 **Background: Prevalence and History**

3 Symptomatology

4 Pathophysiological hallmarks

5 Tau Tangles

6 Amyloid plaques

7 Risk factors

8 Treatment approaches

9 Diagnostics and Biomarkers

Alzheimer's Disease

- Alzheimer's Disease (AD) "is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. It is the most common cause of dementia in older adults. While dementia is more common as people grow older, it is not a normal part of aging" *National Institute of Aging*

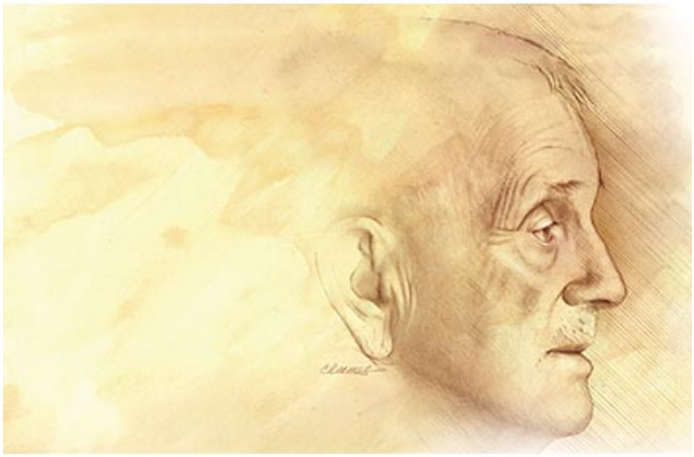
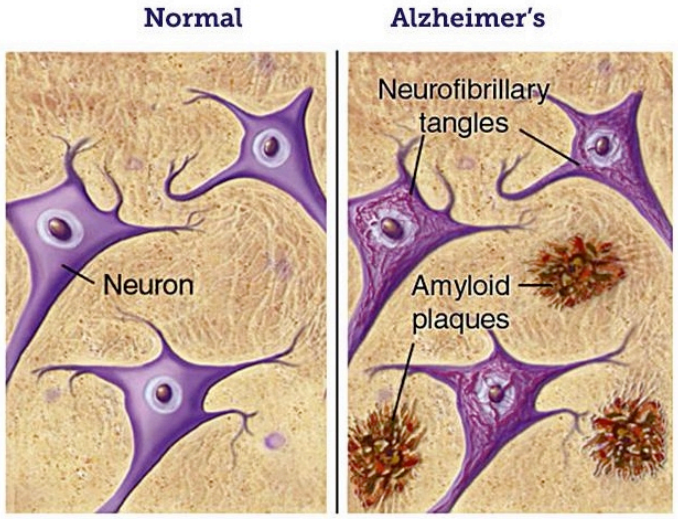


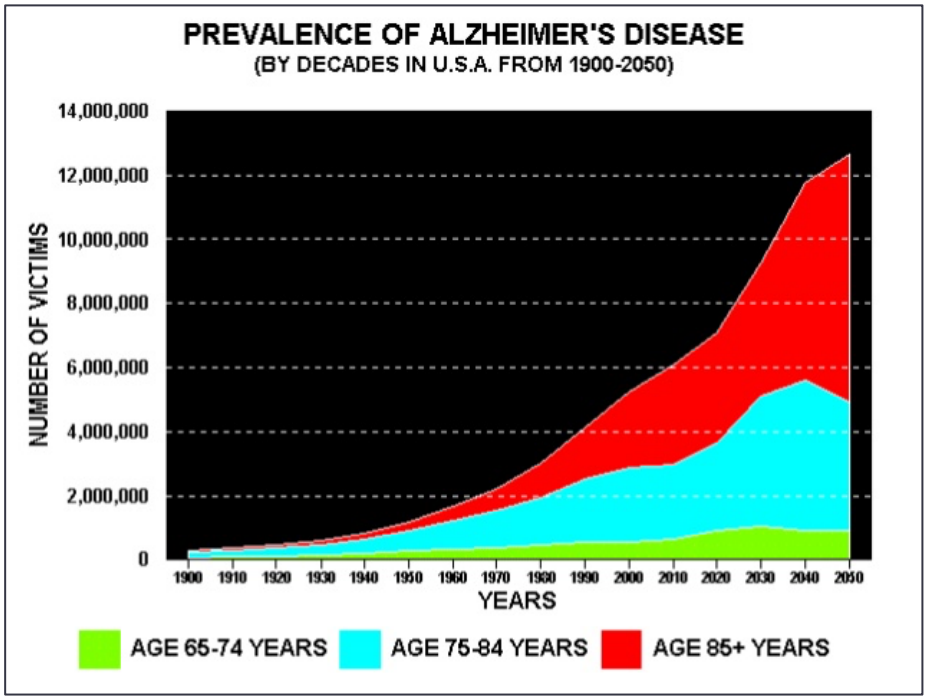
Illustration courtesy of the Alzheimer's Disease Education and Referral Center, a service of the National Institute on Aging

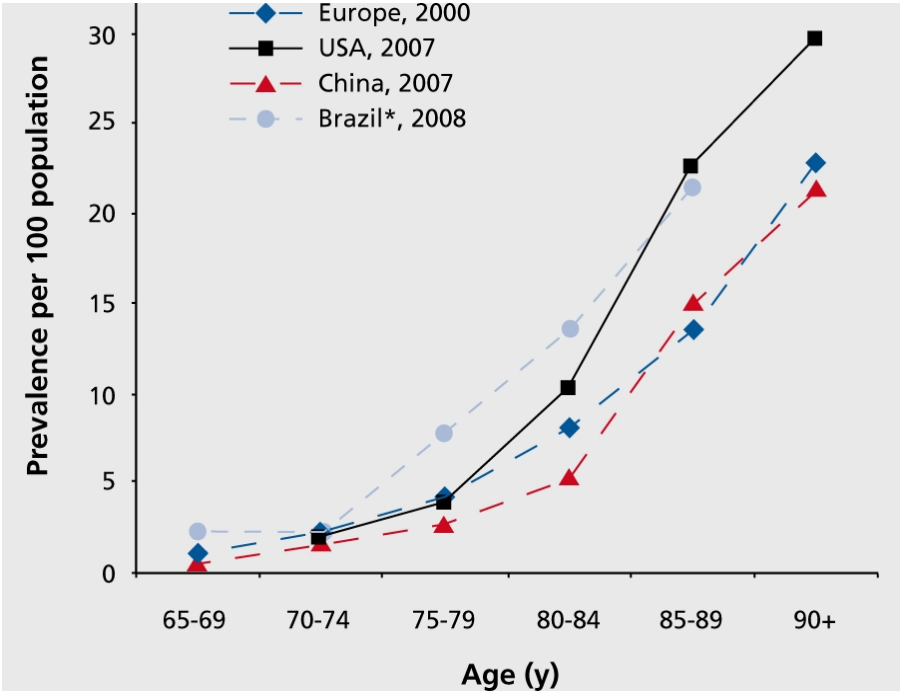
- AD causes deterioration of brain nerve cells and ultimately death.

- **The deterioration is caused by:**
  - Severe neurodegeneration (i.e., **neuronal loss**).
  - Build up of abnormal substances called **amyloid plaques.**
  - Build up of abnormal substances called **neurofibrillary tangles**.



Prevalence



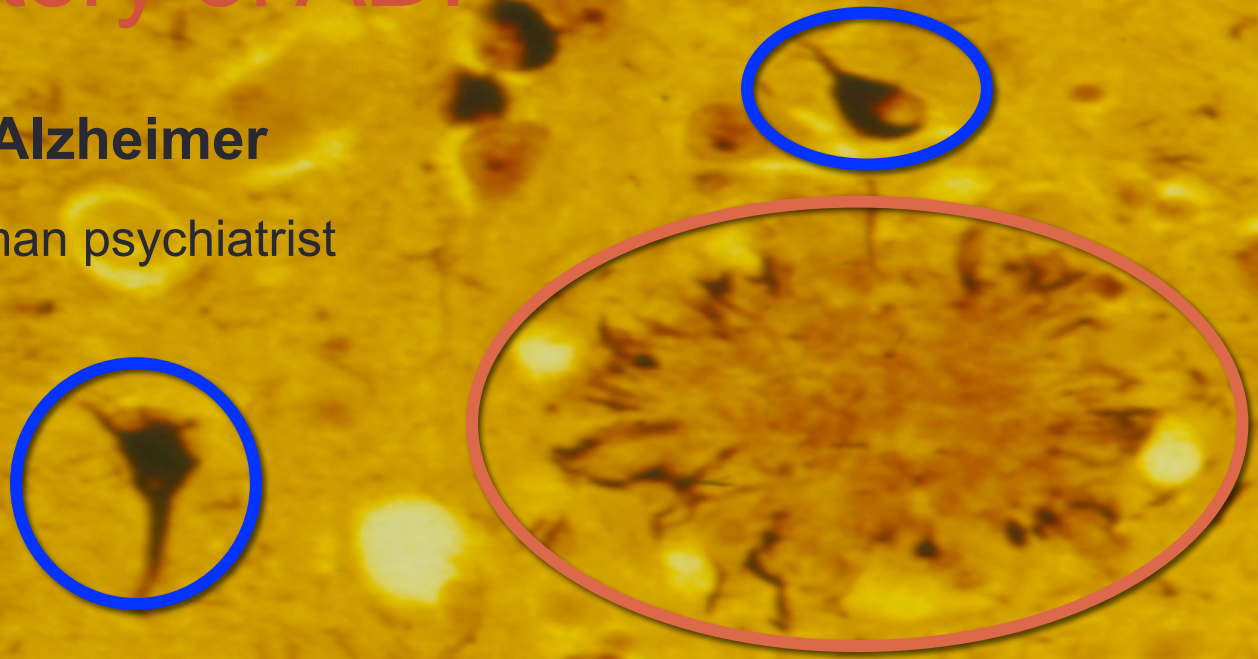


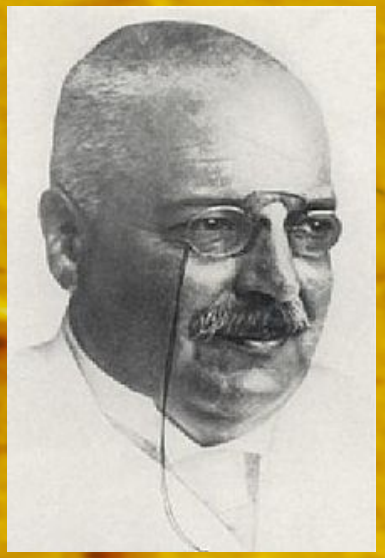
Impact of AD

- AD is the 7th leading cause of death in the U.S. (Heart Disease is #1)
- Length of the disease is 3 – 20 years (average 9y)
- By 2029 all Baby Boomers (1946-1964) will be at least 65 – 10 million of the 78 million are predicted to develop AD.
- 2010 Cost of Care is estimated at $172 billion (Healthcare and Long Term Care)
- Other economic costs:
  - Cost to businesses – lost work time, absenteeism, leaves of absence, quitting work.

History of AD:

- **Alois Alzheimer**
  - German psychiatrist





1864-1913

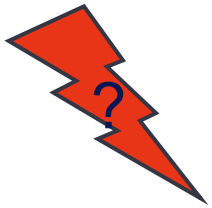
Auguste Deter
1851-1906

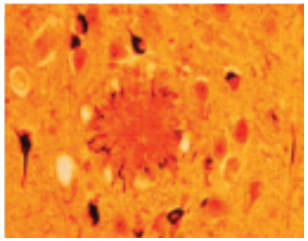
- Described symptoms + pathology
  - Neuronal loss
  - **Plaques**
  - **Tangles**
- Patient Mrs. Auguste Deter

Alzheimer first met his now famous patient, Mrs Deter, on November 26, 1901. She had been admitted the day before to municipal mental asylum in Frankfurt. She was sitting on the bed with a helpless expression. According to the husband, the couple had been harmoniously married since 1873, but he had recently noticed a gradual decline in his wife. Her symptoms began at age 51 years. For 8 months she had been developing progressive changes in her personality. She presented with ideas of jealousy toward her husband, a rapidly worsening memory weakness and pronounced psychosocial impairment; sometimes she felt that someone wanted to kill her and began to shout wildly. At the clinic, she was disorientated to time and place and confused. Over time, her state generally worsened. Her speech became completely unintelligible. In her final year, she was totally apathetic and spent most of her time in bed with legs pulled up.

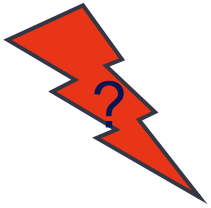
Auguste Deter
1851-1906

"what is the relationship between protein aggregation and neurodegeneration?"

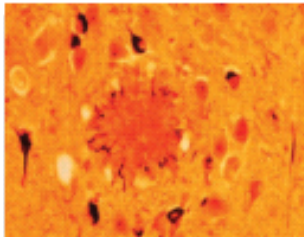




Disease



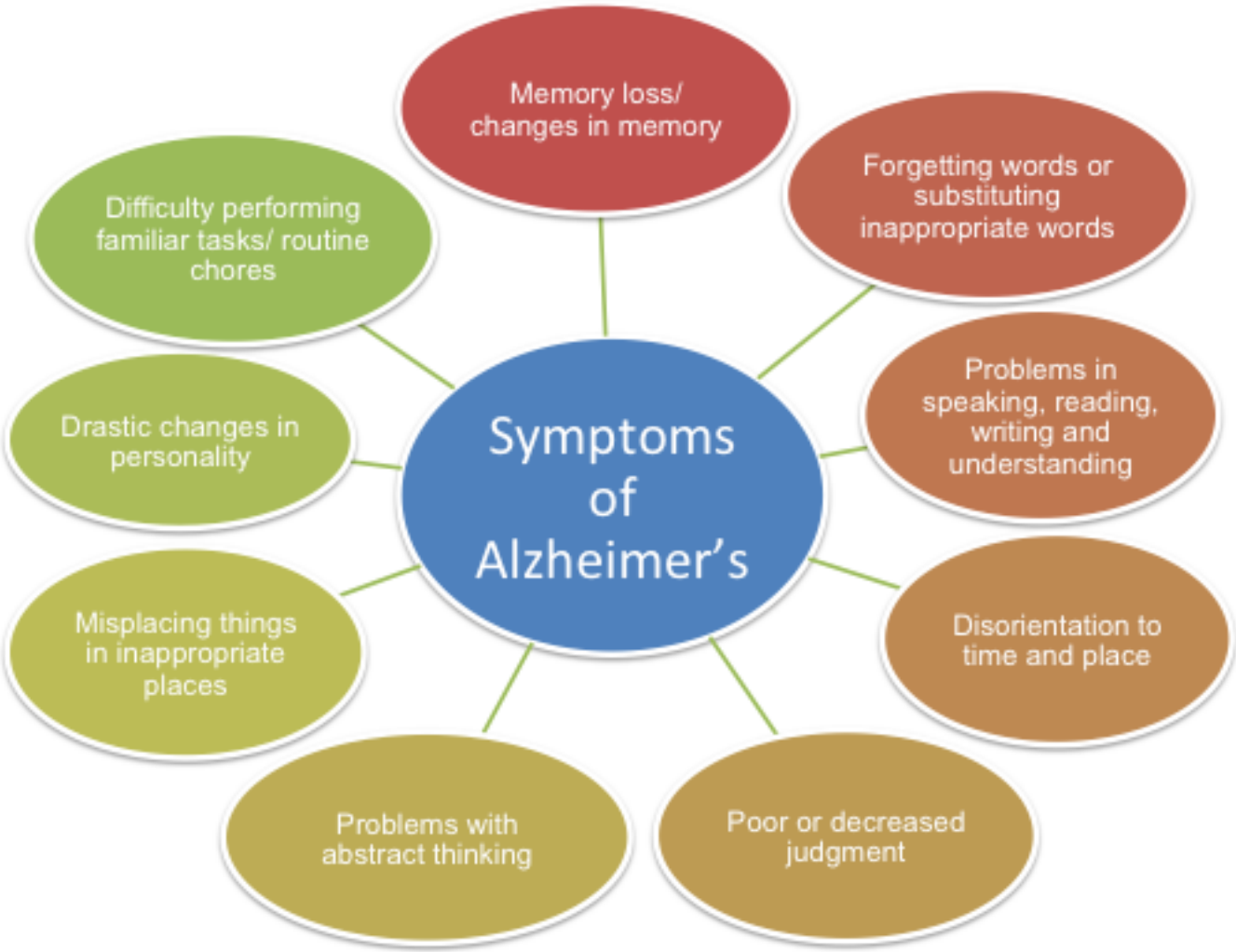
Disease



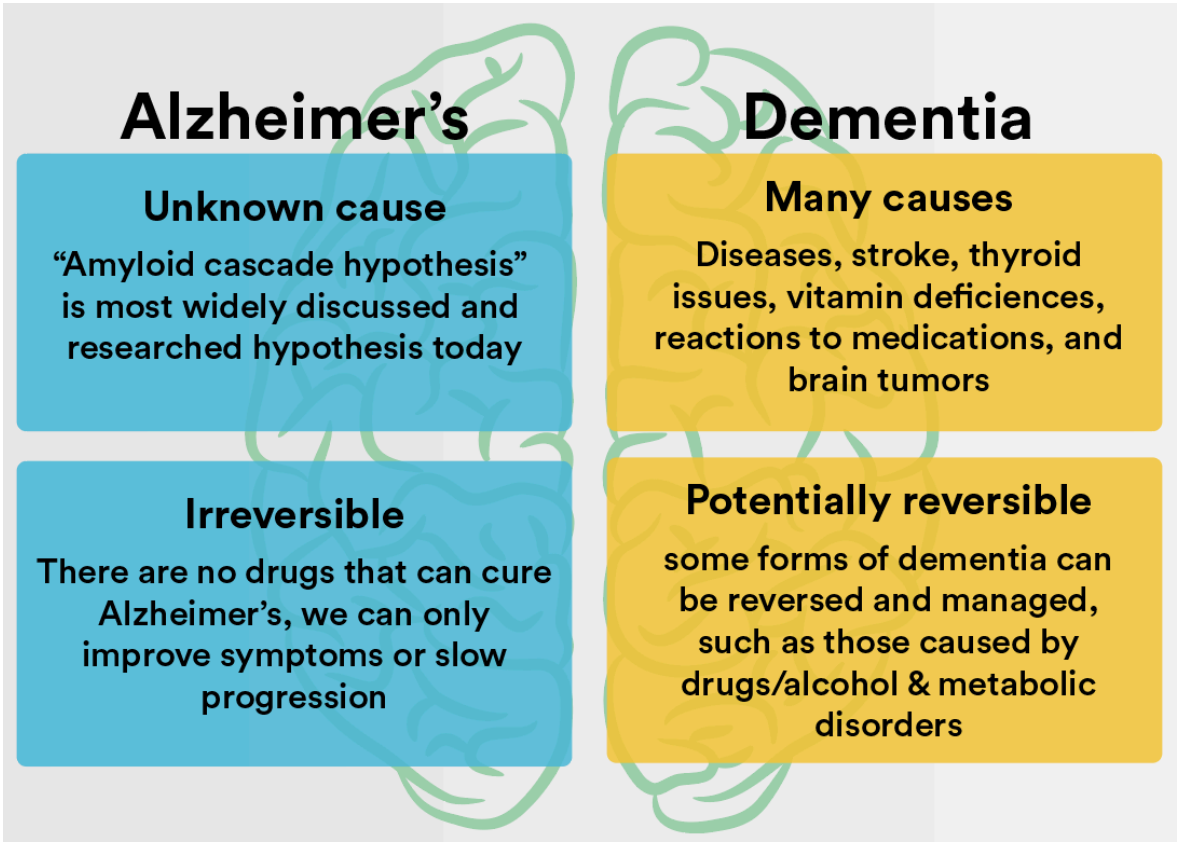
Alzheimer's Disease – Overview

1. Test your knowledge about Alzheimer's disease
2. Background: Prevalence and History
3. **Symptomatology**
4. Pathophysiological hallmarks
5. Amyloid plaques
6. Tau Tangles
7. Risk factors
8. Treatment approaches
9. Diagnostics and Biomarkers

Symptomatology



What is the difference between Dementia and Alzheimer's disease?



Dementia is a syndrome in which there is deterioration in memory, thinking *(beyond what might be expected from normal ageing)*, behaviour and the ability to perform everyday activities. *WHO*

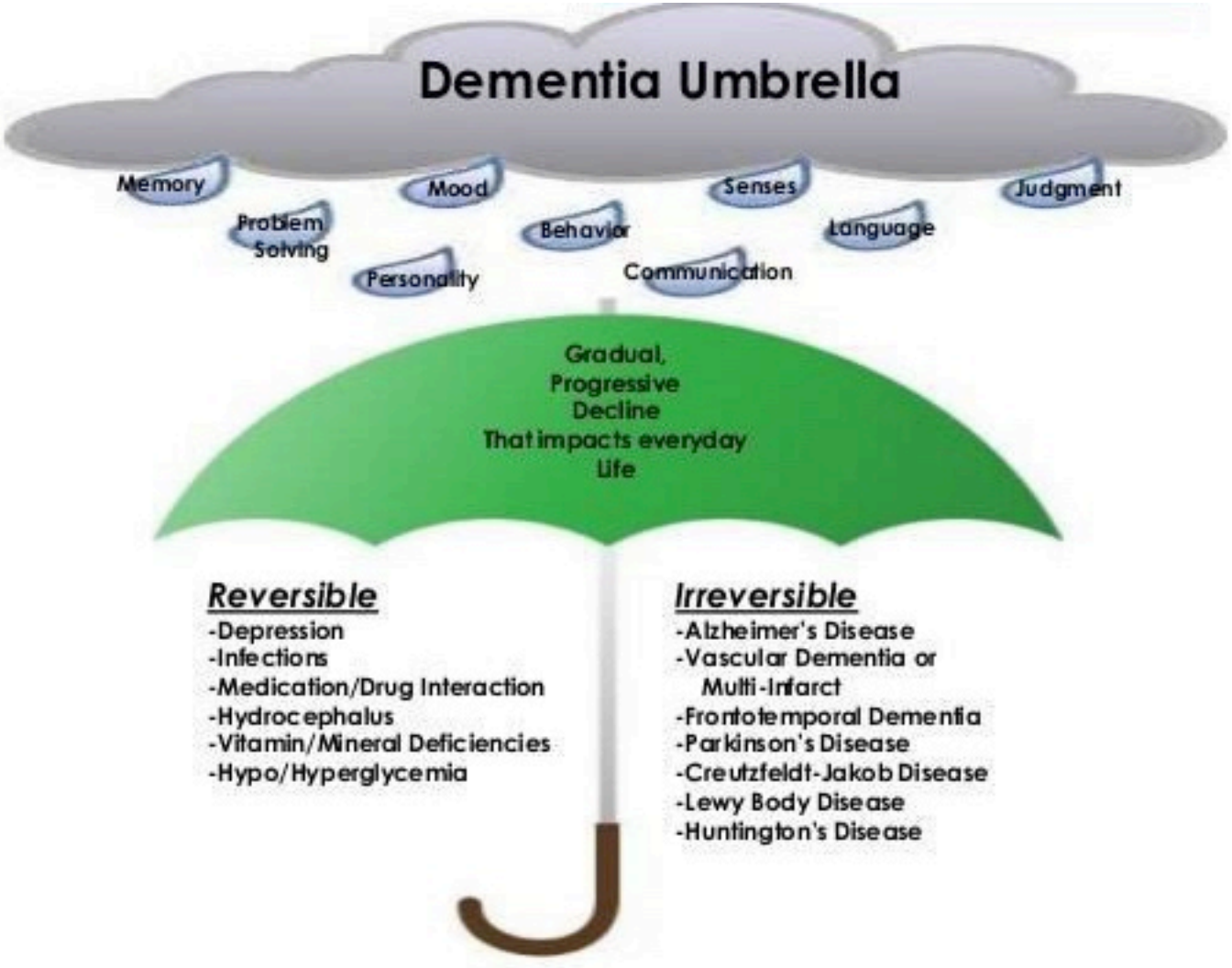
Dementia is one of the major causes of disability and dependency among older people worldwide.

Dementia has physical, psychological, social, and economical impact on carers, families and society.

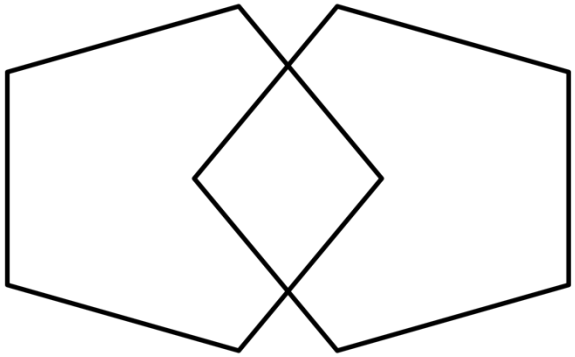
https://www.kindlycare.com/dementia-vs-alzheimers/

http://www.who.int

Reversible Dementia



Mini mental state examination test

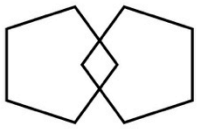


MINI MENTAL STATE EXAMINATION (MMSE)

Name:

DOB:

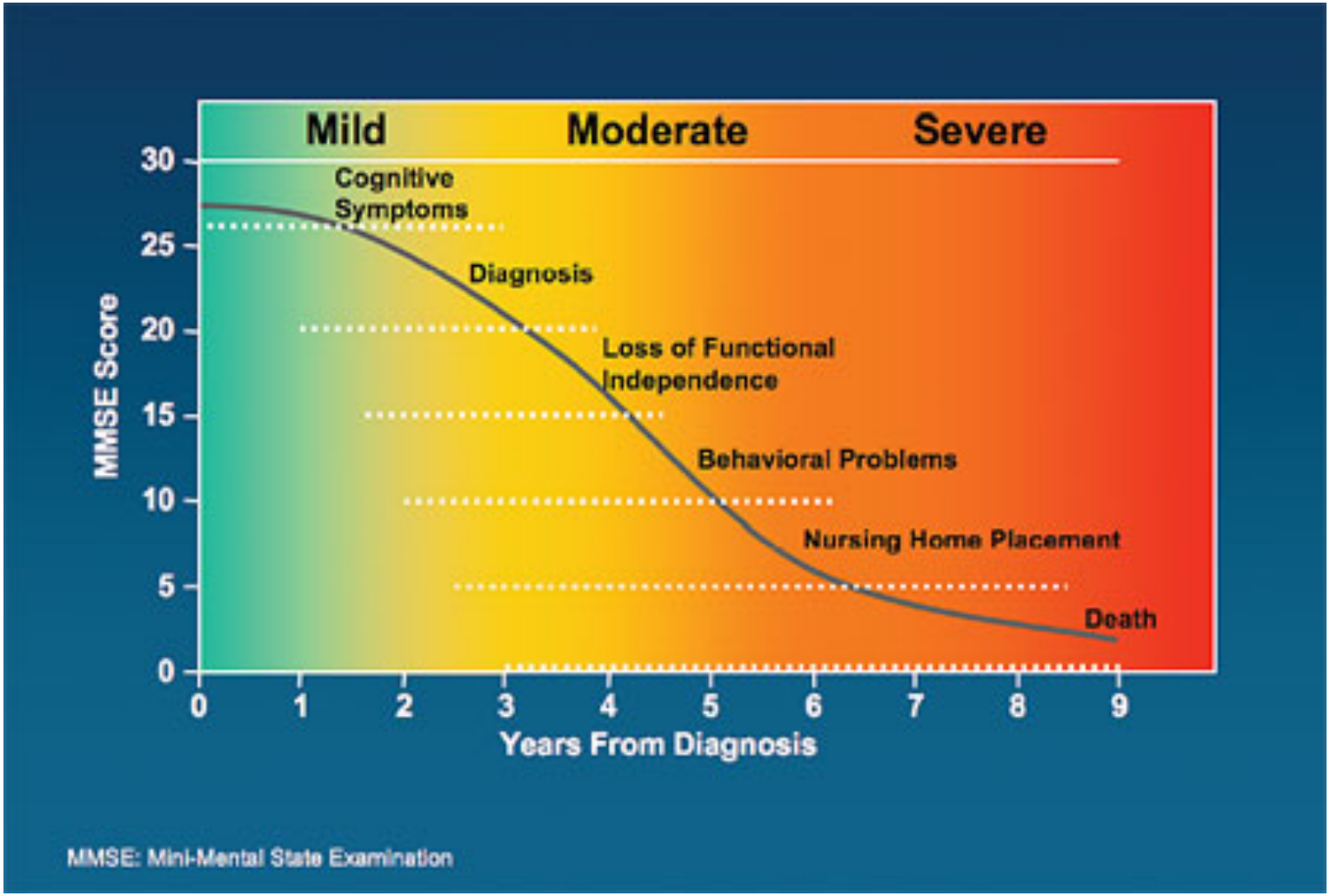
Hospital Number:

One point for each answer	DATE:		
ORIENTATION Year Season Month Date Time	...../ 5	...../ 5	...../ 5
Country Town District Hospital Ward/Floor	...../ 5	...../ 5	...../ 5
REGISTRATION Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).	...../ 3	...../ 3	...../ 3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell "WORLD" backwards: DLROW).	...../ 5	...../ 5	...../ 5
RECALL Ask for the names of the three objects learned earlier.	...../ 3	...../ 3	...../ 3
LANGUAGE Name two objects (e.g. pen, watch).	...../ 2	...../ 2	...../ 2
Repeat "No ifs, ands, or buts".	...../ 1	...../ 1	...../ 1
Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear").	...../ 3	...../ 3	...../ 3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".	...../ 1	...../ 1	...../ 1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.	...../ 1	...../ 1	...../ 1
COPYING: Ask the patient to copy a pair of intersecting pentagons 	...../ 1	...../ 1	...../ 1
TOTAL:	...../ 30	...../ 30	...../ 30

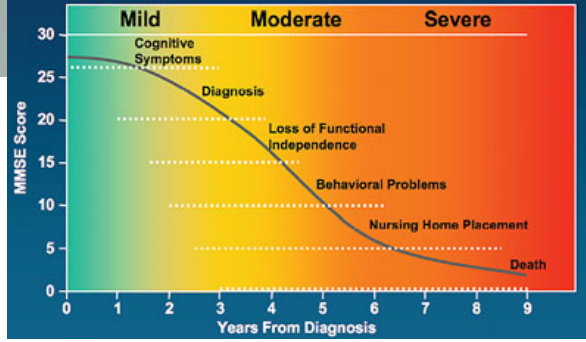
MMSE scoring
24-30: no cognitive impairment
18-23: mild cognitive impairment
0-17: severe cognitive impairment

OME Oxford Medical Education

Cognitive decline

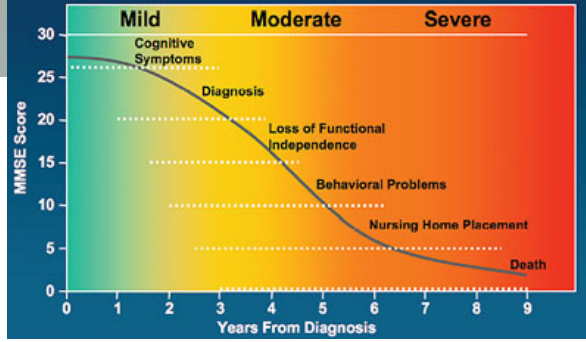


Stages of cognitive decline



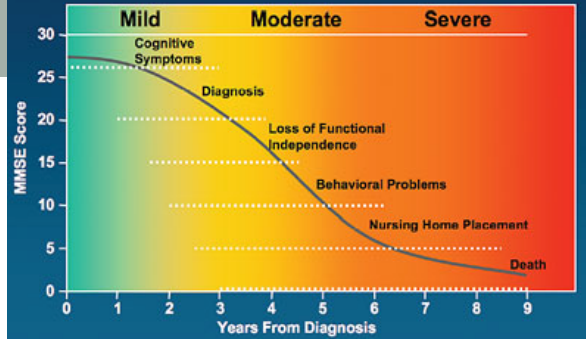
- **Mild or Early Stage (Mild cognitive impairment)**
  - Friends, family or co-workers begin to notice deficiencies:
    - Word finding problems
    - Decreased ability to remember names
    - Performance issues in social or work settings
    - Reading a passage and retaining little material
    - Losing or misplacing a valuable object
    - Decline in ability to plan or organize

Stages of cognitive decline



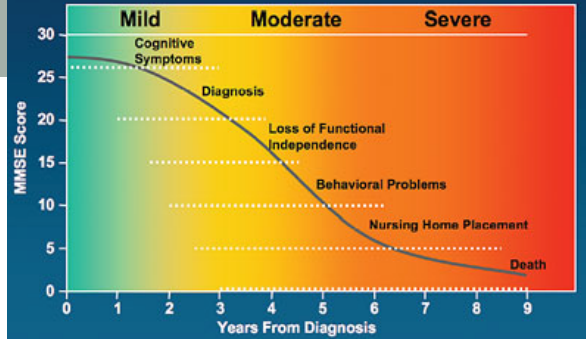
- **Moderate or Middle Stage**
  - Major gaps in memory and deficits in cognitive function emerge.
  - Assistance with day-to-day activities becomes essential.
  - Deficits include:
    - Inability to recall important details such as their current address, their telephone number.
    - Confused about where they are or about the date, day of the week or season.
    - Need help choosing proper clothing for the season or the occasion.
    - May have increasing episodes of urinary or fecal incontinence and need assistance with toileting and personal care.

Stages of cognitive decline



- **Moderate or Middle Stage**
  - Lose most awareness of recent experiences and events as well as of their surroundings.
  - Tend to wander and become lost.
  - Experience significant personality changes and behavioral symptoms.
  - Including suspiciousness and delusions (for example, believing that their caregiver is an impostor)
  - Hallucinations (seeing or hearing things that are not really there)
  - Compulsive, repetitive behaviors such as hand-wringing or tissue shredding

Stages of cognitive decline



- **Severe or late stage**
  - Need full assistance with eating and toileting; general incontinence.
  - Frequent loss of recognizable speech, although words or phrases may occasionally be uttered.
  - Reflexes become abnormal and muscles grow rigid
  - Individuals lose the ability to:
    - walk without assistance
    - sit without support
    - hold their head up
    - swallowing

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1 Test your knowledge about Alzheimer's disease

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3 Symptomatology

4 **Pathophysiological hallmarks**

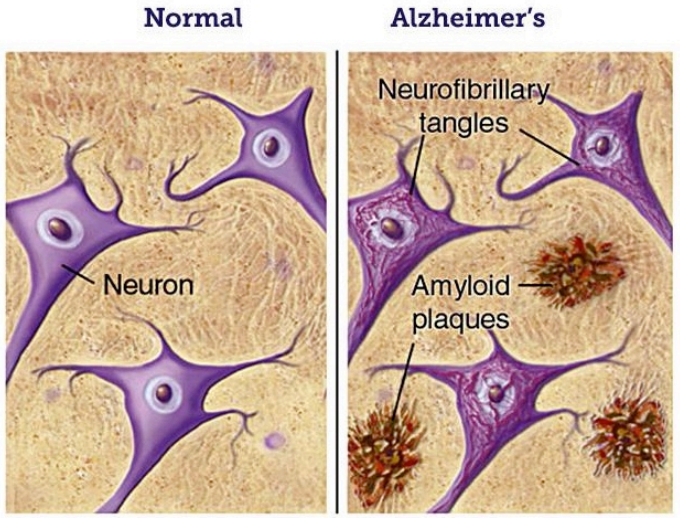
5 Amyloid plaques

6 Tau Tangles

7 Risk factors

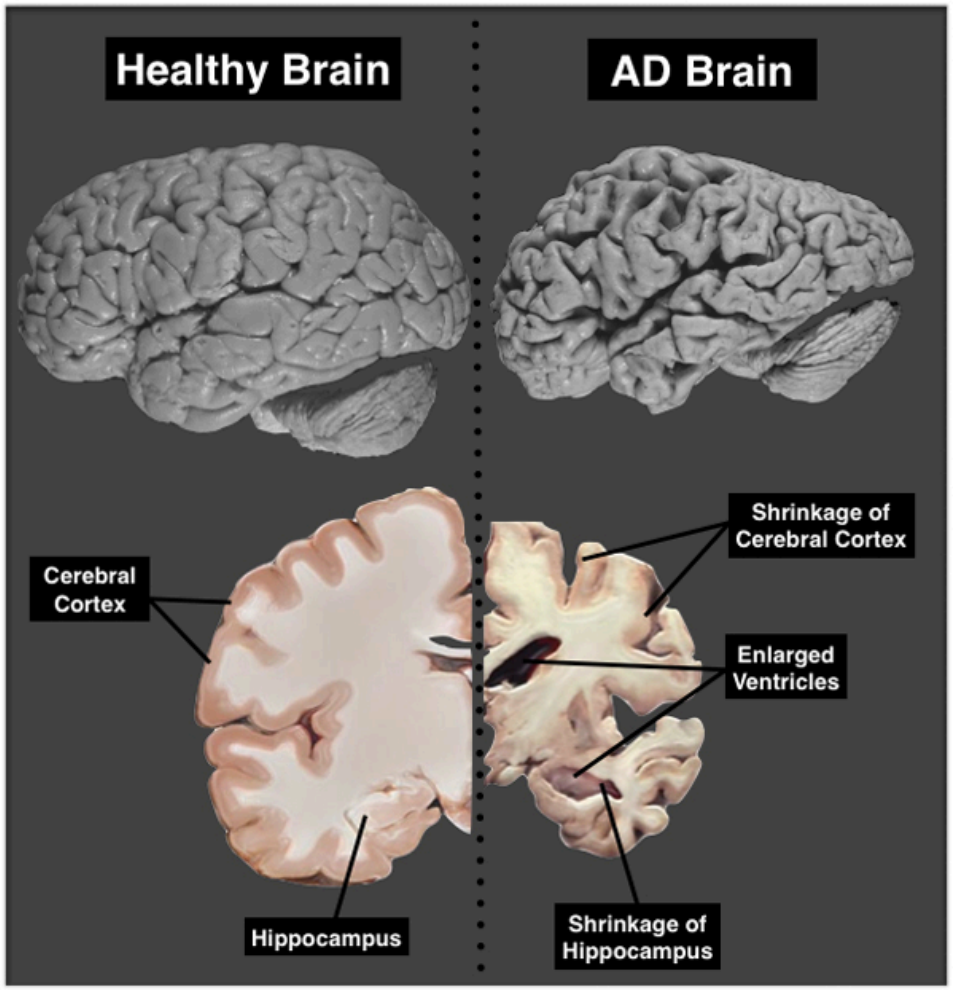
8 Treatment approaches

9 Diagnostics and Biomarkers



Pathophysiological hallmarks

1) Neuronal loss:
   - Retraction (shriveling) of the **cortex**: Damaging areas involved in thinking, planning and remembering.
   - Shrinkage is especially severe in the **hippocampus**, a brain area that plays a key role in formation of new memories.
   - **Ventricles** (cerebrospinal fluid-filled spaces within the brain) grow large



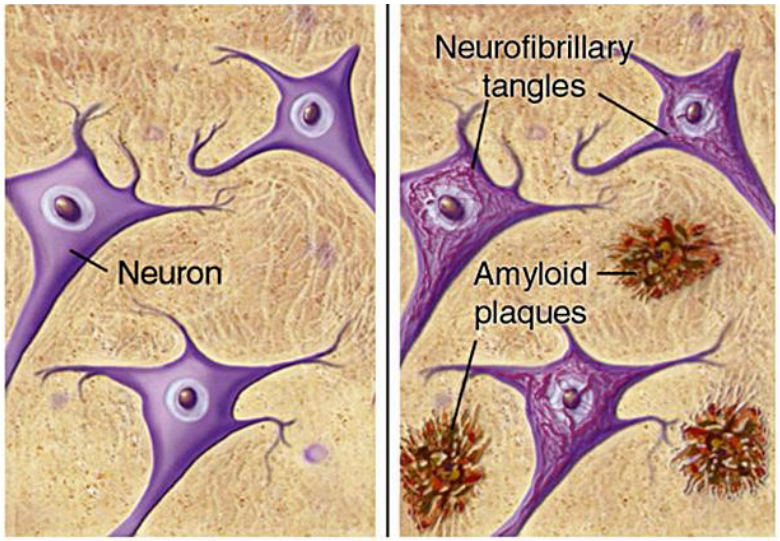
Pathophysiological hallmarks

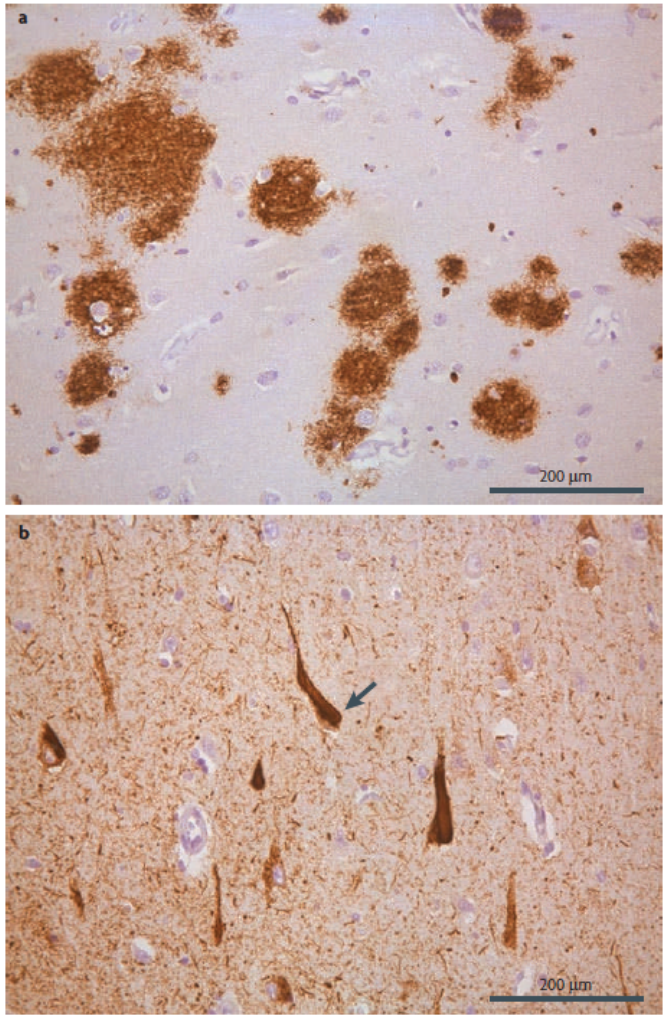
2) Amyloid plaques

= extracellular aggregates of β-amyloid

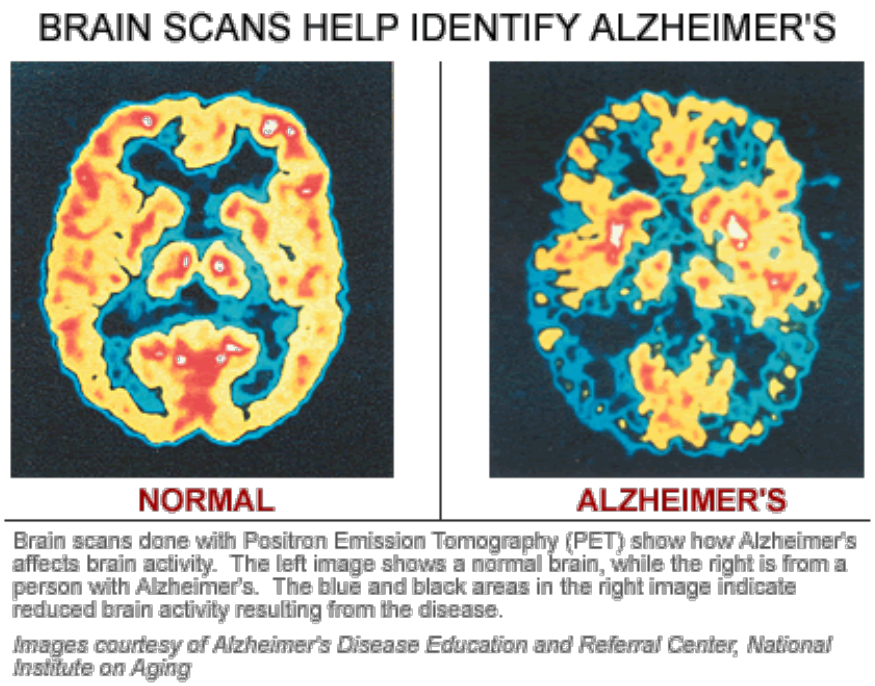
3) Neurofibrillary tangles

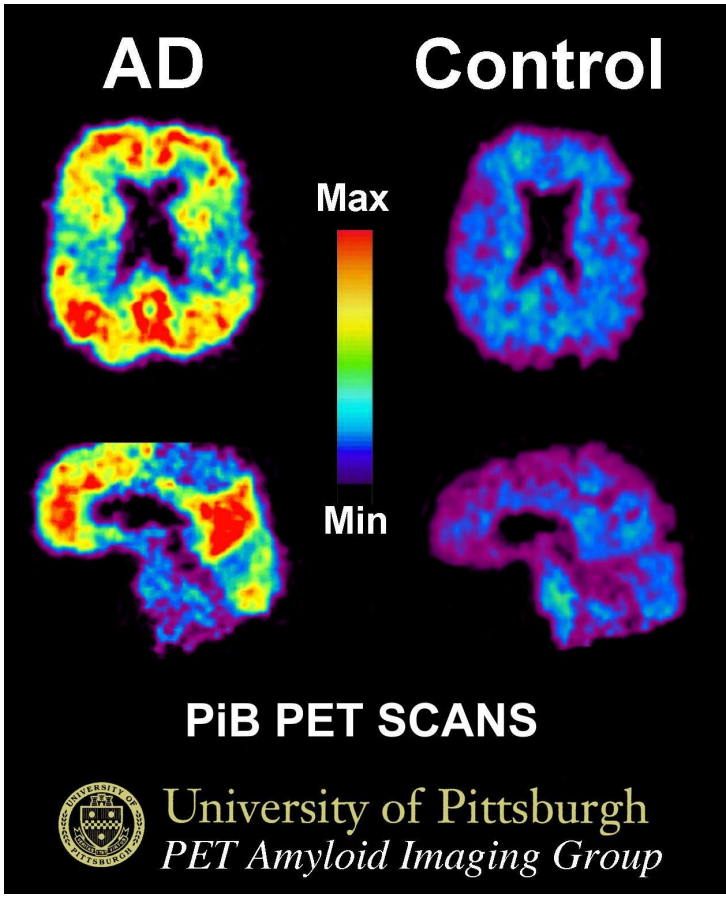
= intracellular accumulation of Tau protein

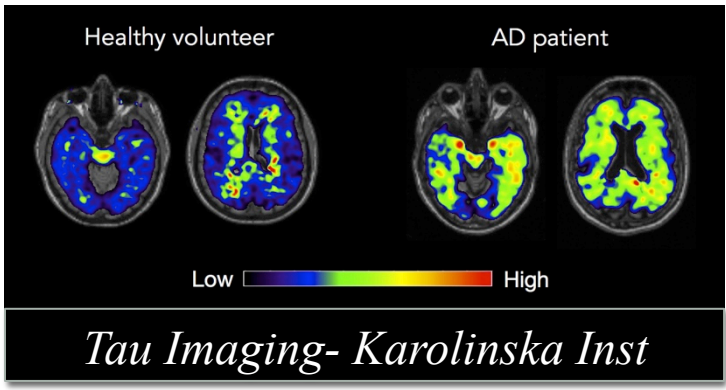




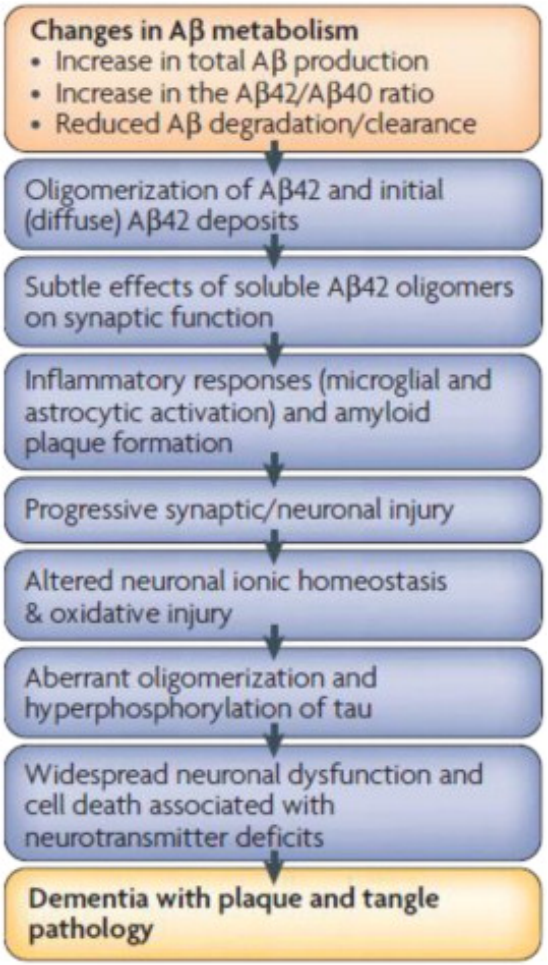
Memory test and PET Scans can help detect early signs of Alzheimer's disease



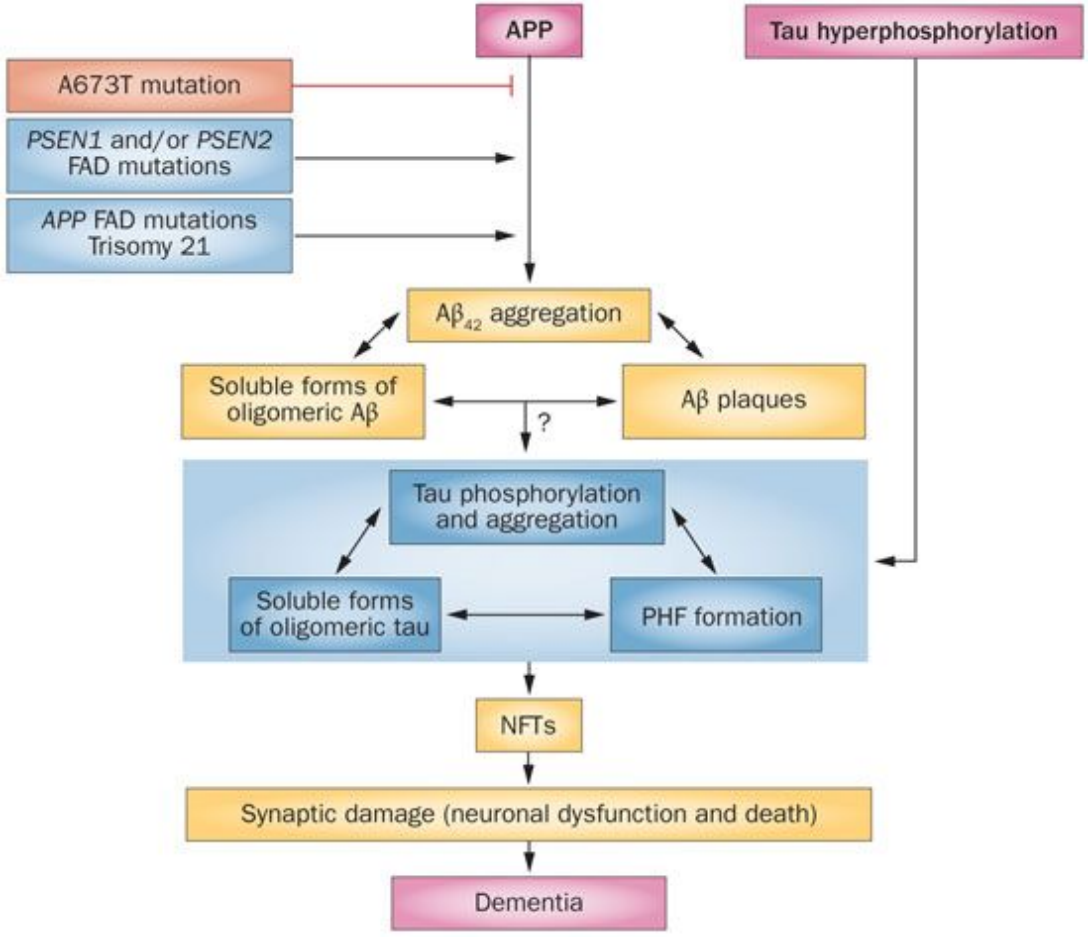




Amyloid Cascade Hypothesis



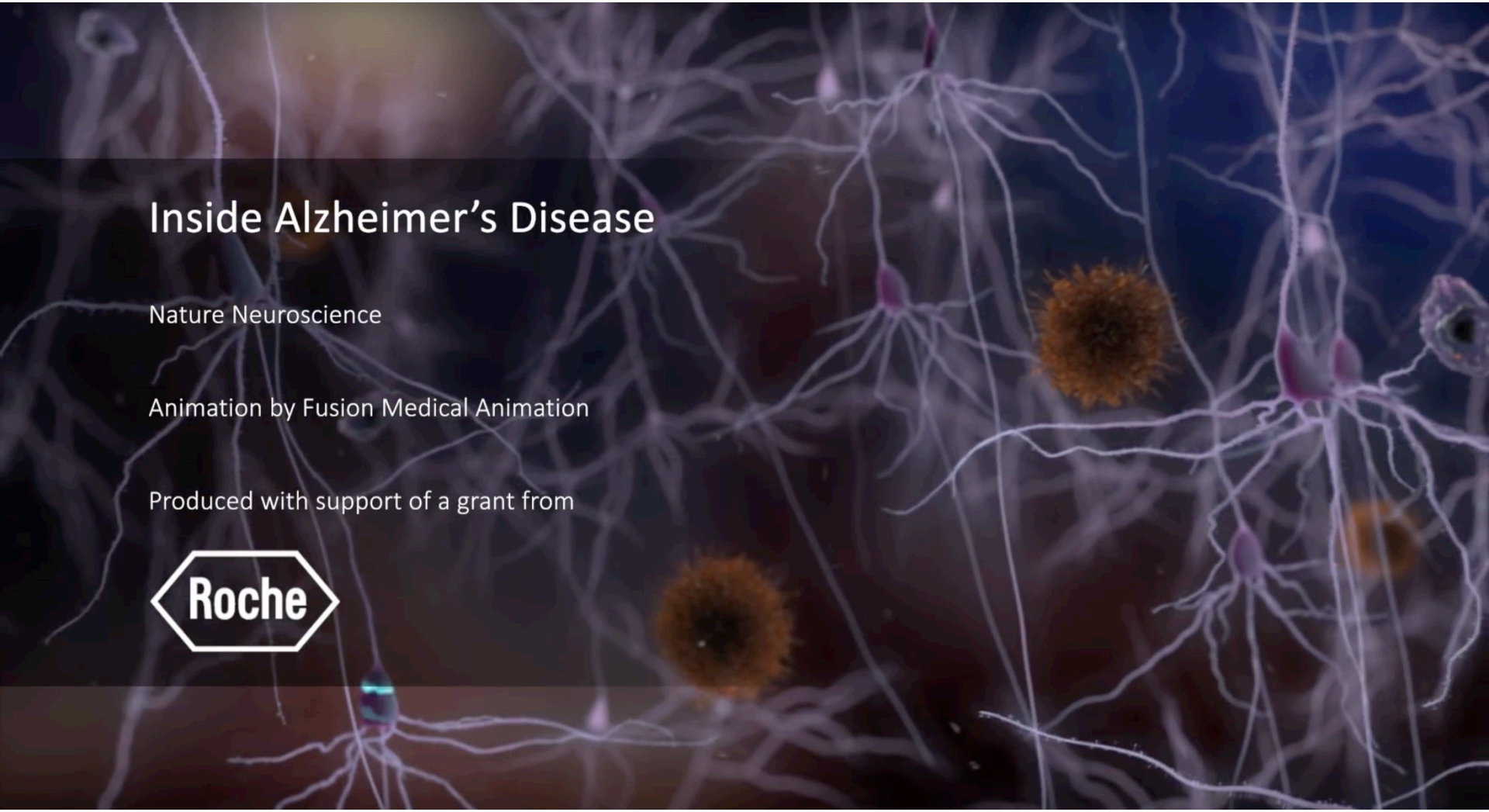
2007



2013

The amyloid (Aβ) cascade hypothesis (Haass and Selkoe, 2007).

Nature Reviews Neurology **9**, 677–686 (2013)

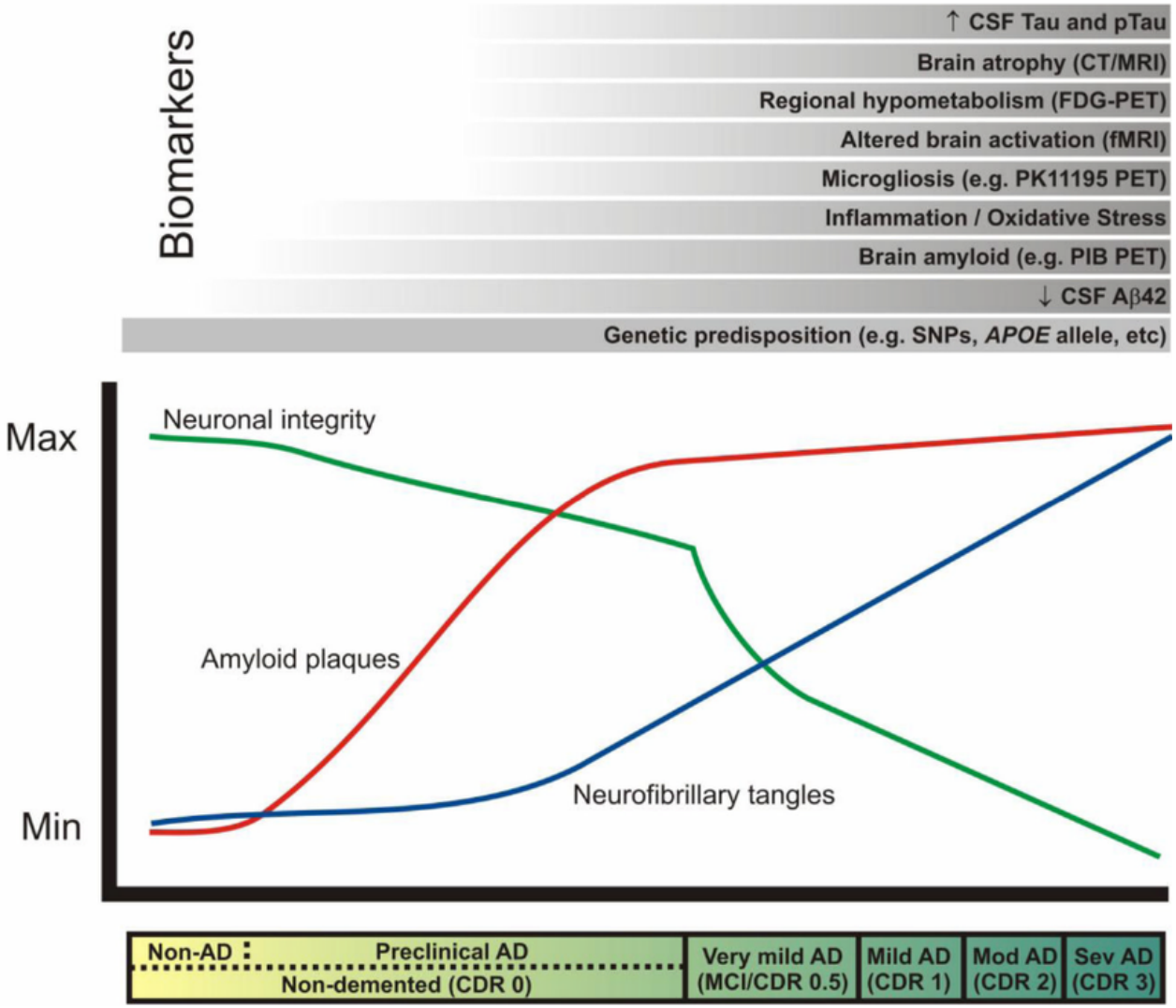


https://www.youtube.com/watch?v=zTd0-A5yDZI

Pathophysiological hallmarks

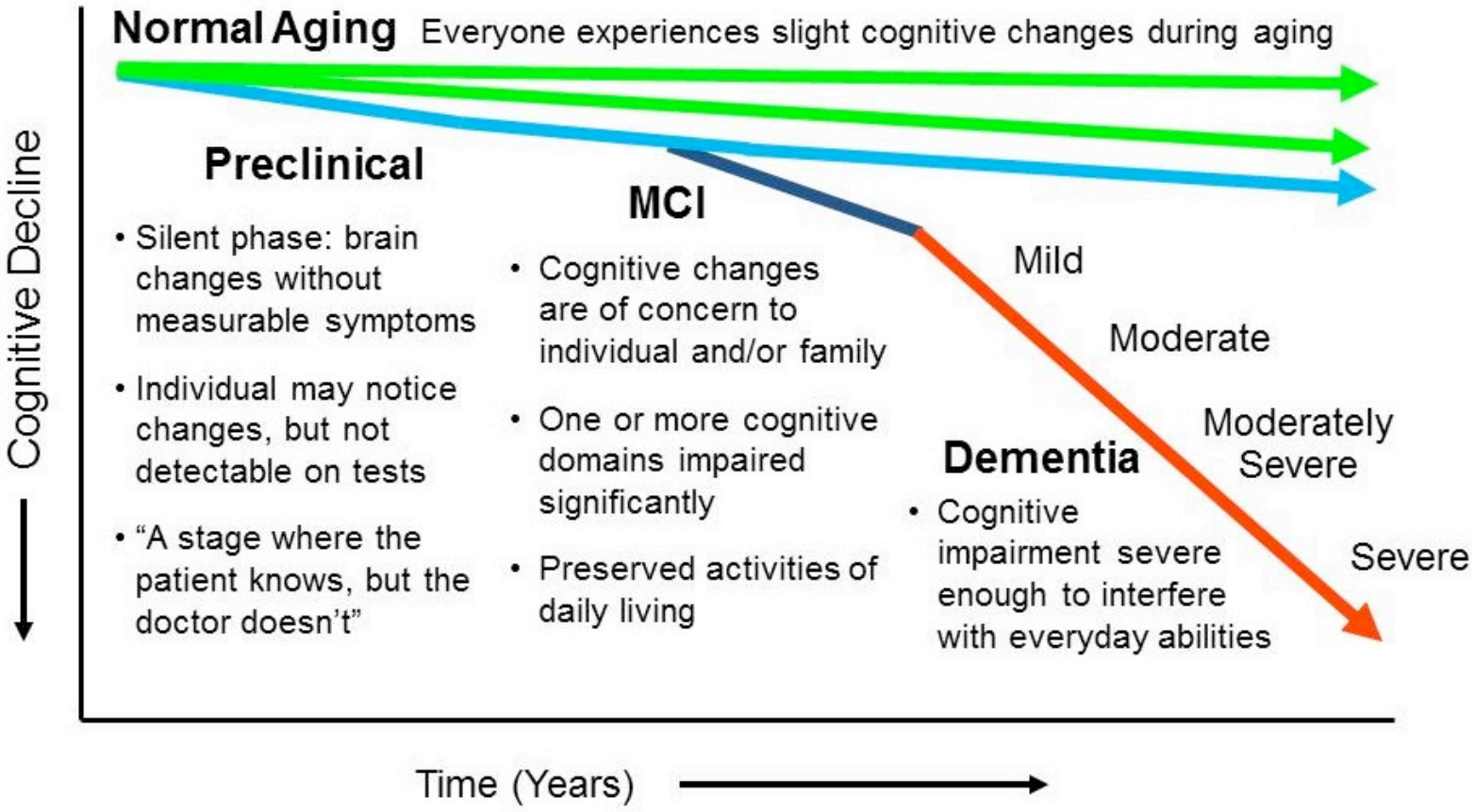
Biomarkers and AD: proposed changes in biomarkers in relation to time course of pathological and clinical stages

Pre-clinical' AD, "Amyloid plaques, and subsequently, NFT, accumulate for ~10-15 years before the synaptic and neuronal loss they accompany manifest as cognitive decline"



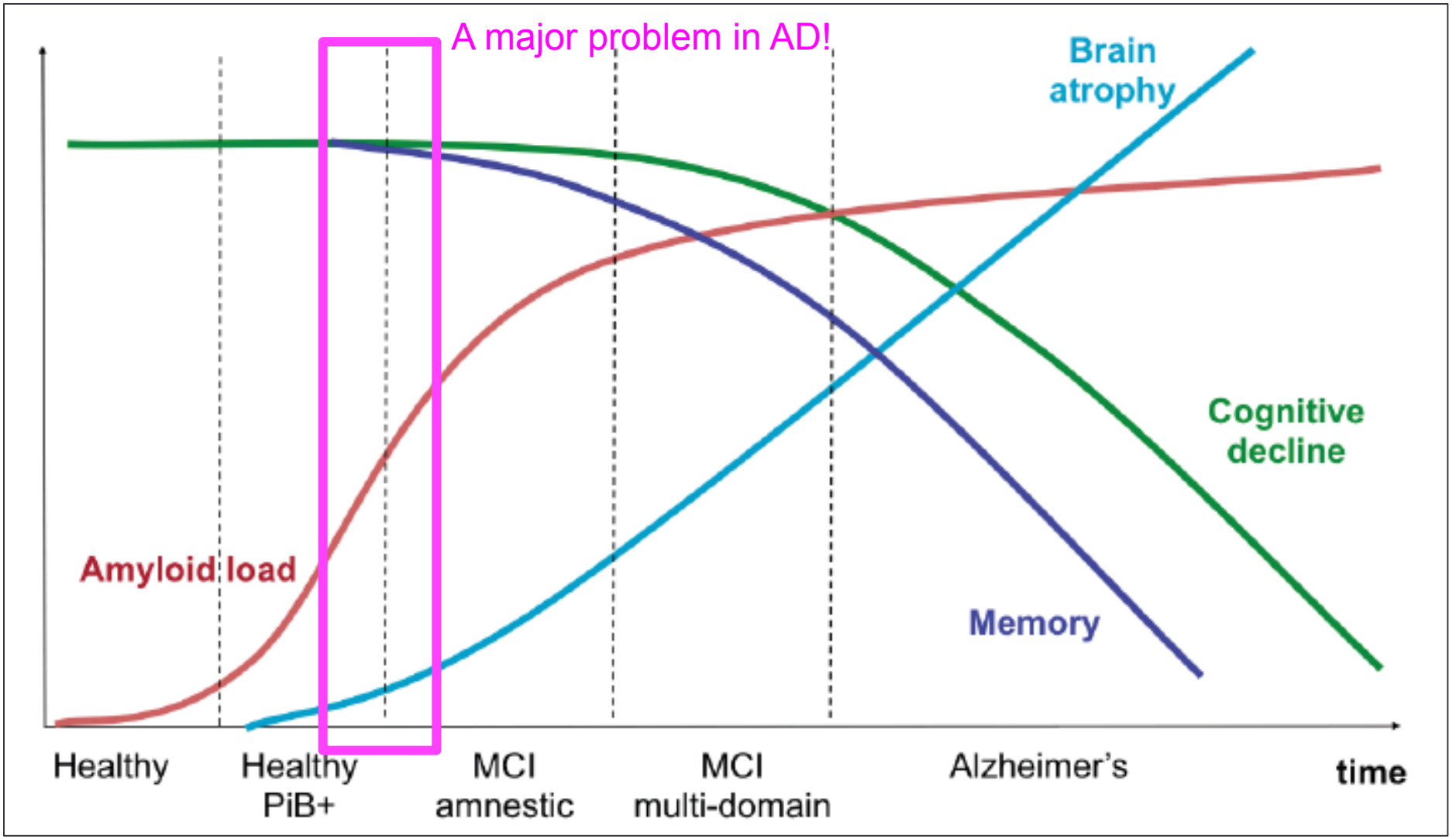
Perrin RJ et al., Nature 2009

Progression from normal aging to Alzheimer's disease or another dementia

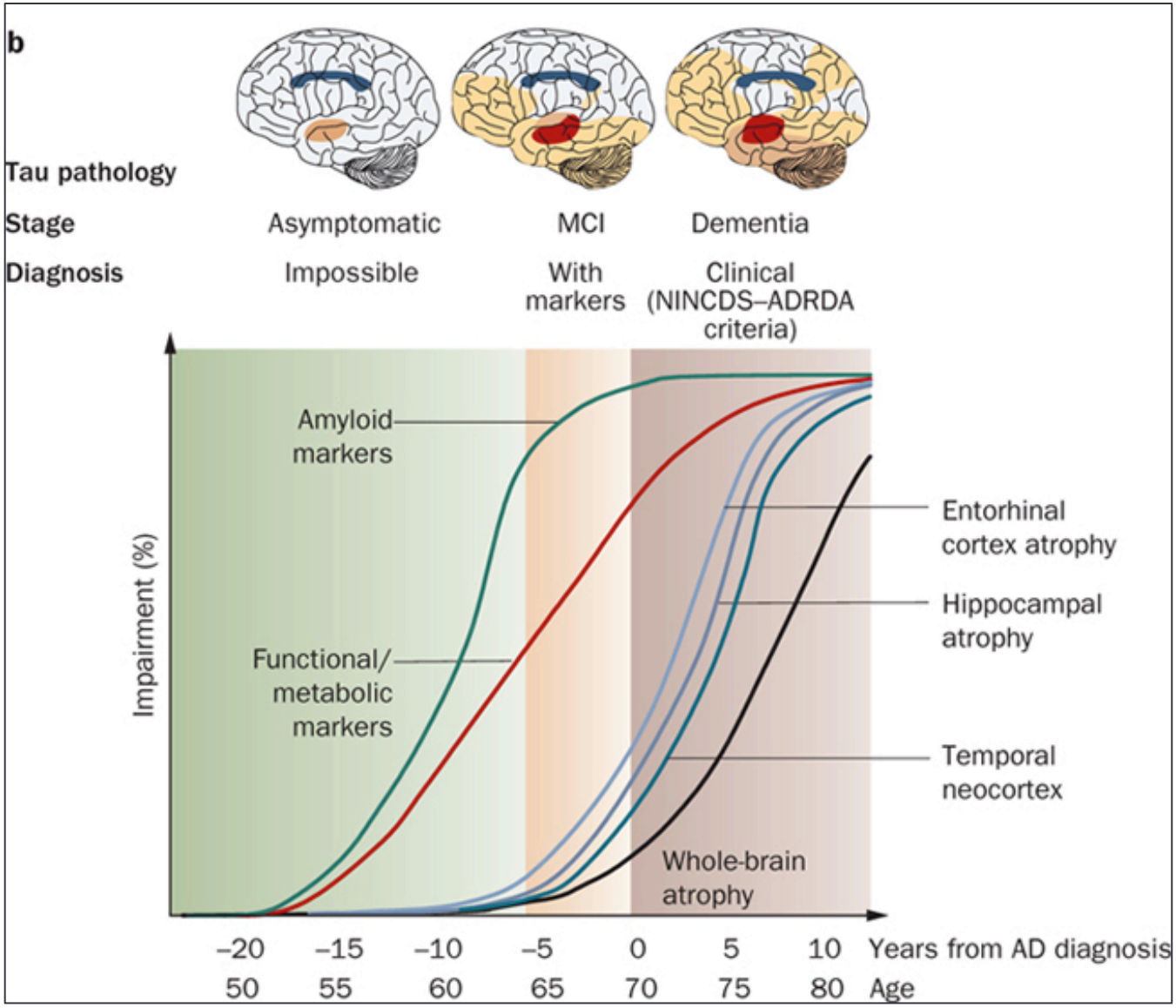


https://www.mind.uci.edu/dementia/mild-cognitive-impairment/

Cognitive decline and brain pathologies

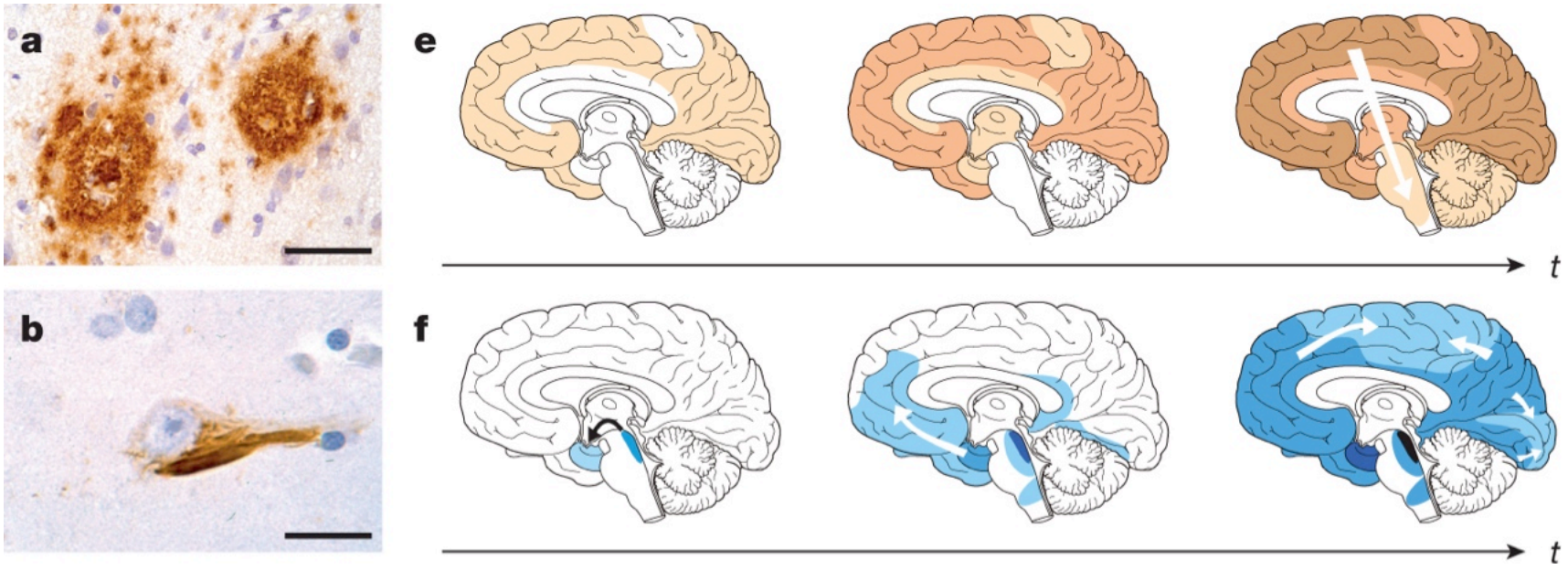


Cognitive decline and brain pathologies



Development of brain pathologies

- Braak and Braak Stages: I-VI
  - Based on spreading of neurofibrillary tangles

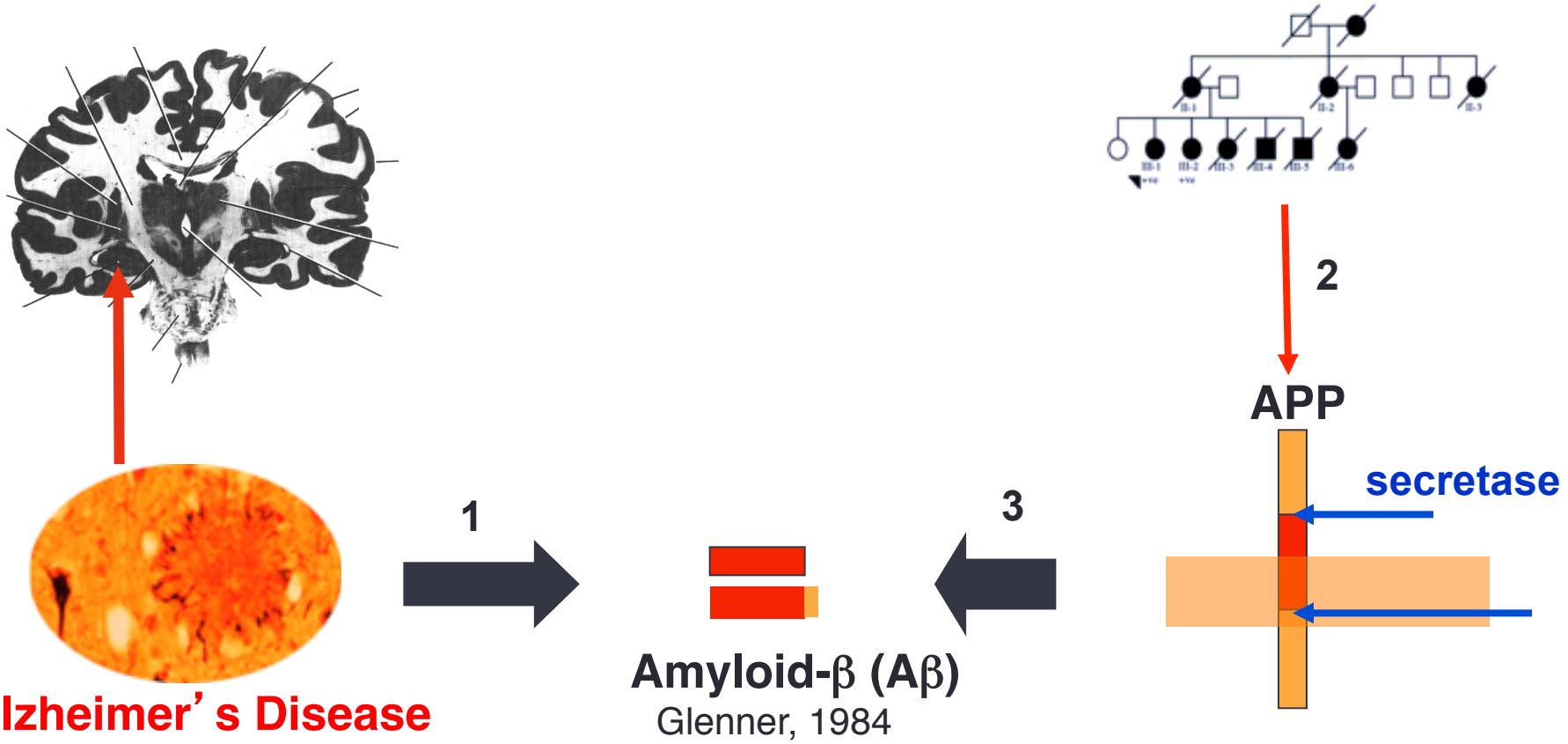


M Jucker & LC Walker *Nature* **501**, 45-51 (2013) doi:10.1038/nature12481

Alzheimer's Disease – Overview

1. Background: Prevalence and History
2. Pathophysiological hallmarks
3. Tau Tangles
4. **Amyloid plaques**
5. Risk factors
6. Treatment approaches
7. Diagnostics

Amyloid Plaques: Neuropathologic and genetic evidence



NON-AMYLOIDOGENIC

No Plaque Formation

AMYLOIDOGENIC

Amyloid Plaque Formation

SAPPα
Neurotrophic and
Neuroprotective

SAPPβ
Not neurotrophic

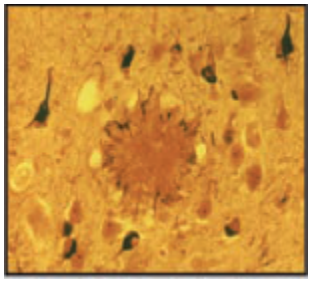
APP

Generation of β-amyloid protein

Aβ
39-42

Aβ
Oligomers

Amyloid Plaques



β

α

γ

γ

p3

AICD

C83

APP

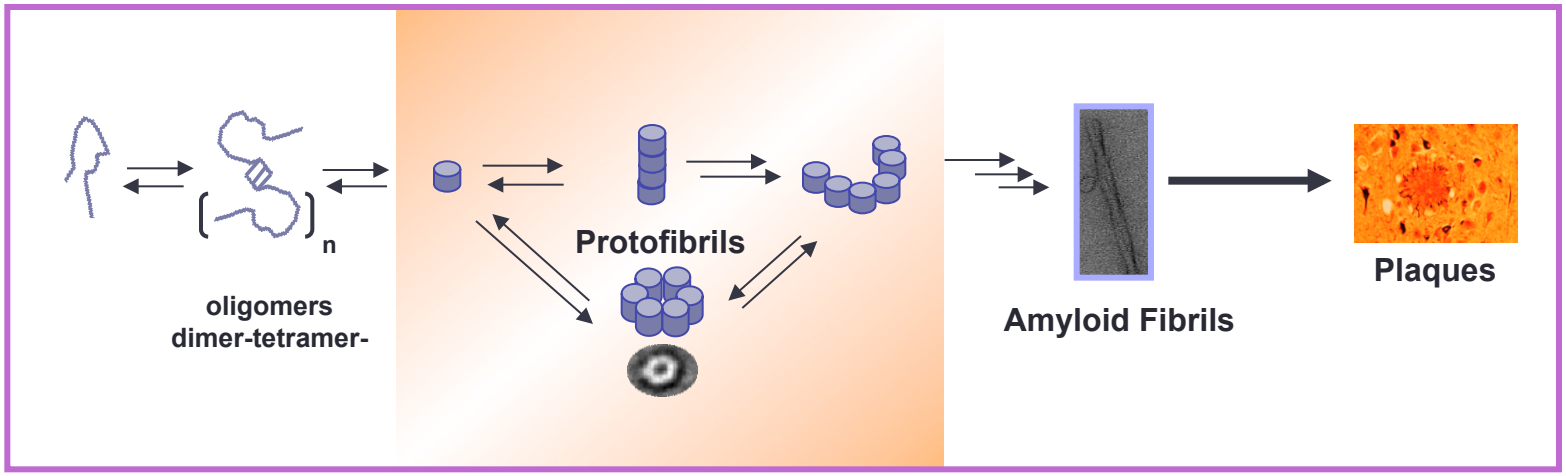
C99

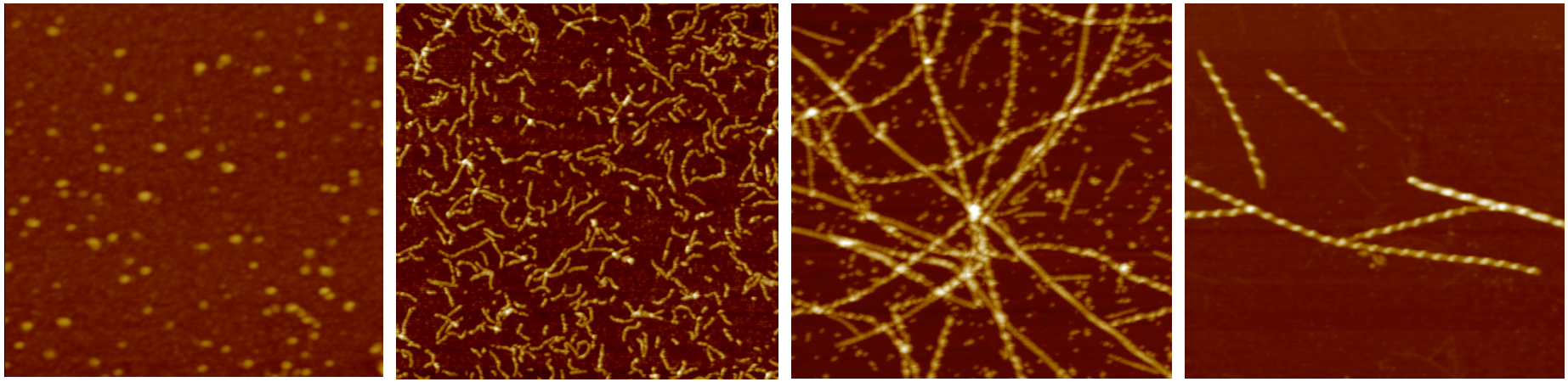
AICD

APP=Amyloid precursor protein
sAPP=soluble APP
CTF=C-terminal fragment
AICS=APP intracellular domain

Generation of β-amyloid protein:

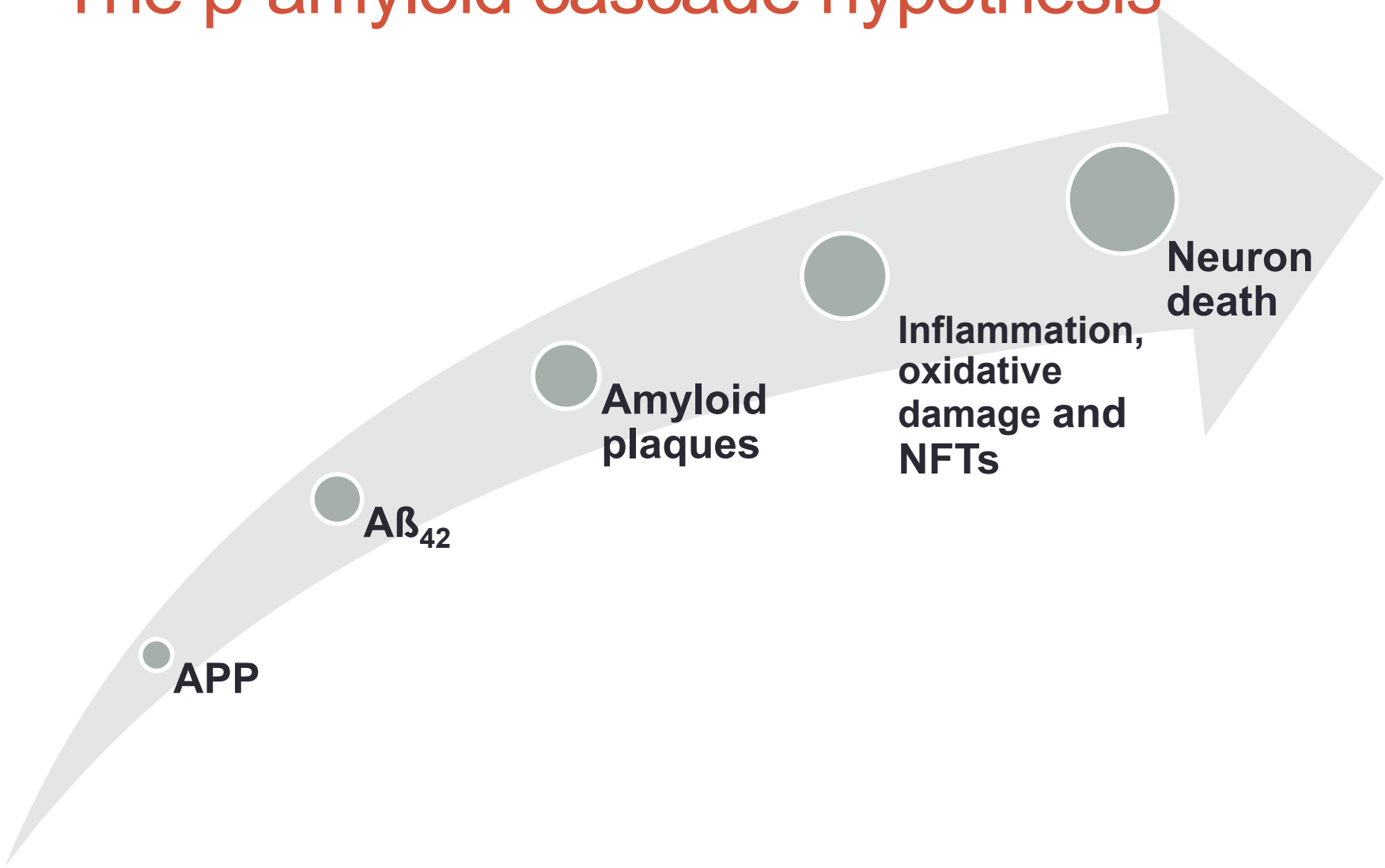
The process of Amyloid Formation plays is the primary cause of neurodegeneration in Alzheimer's Disease.



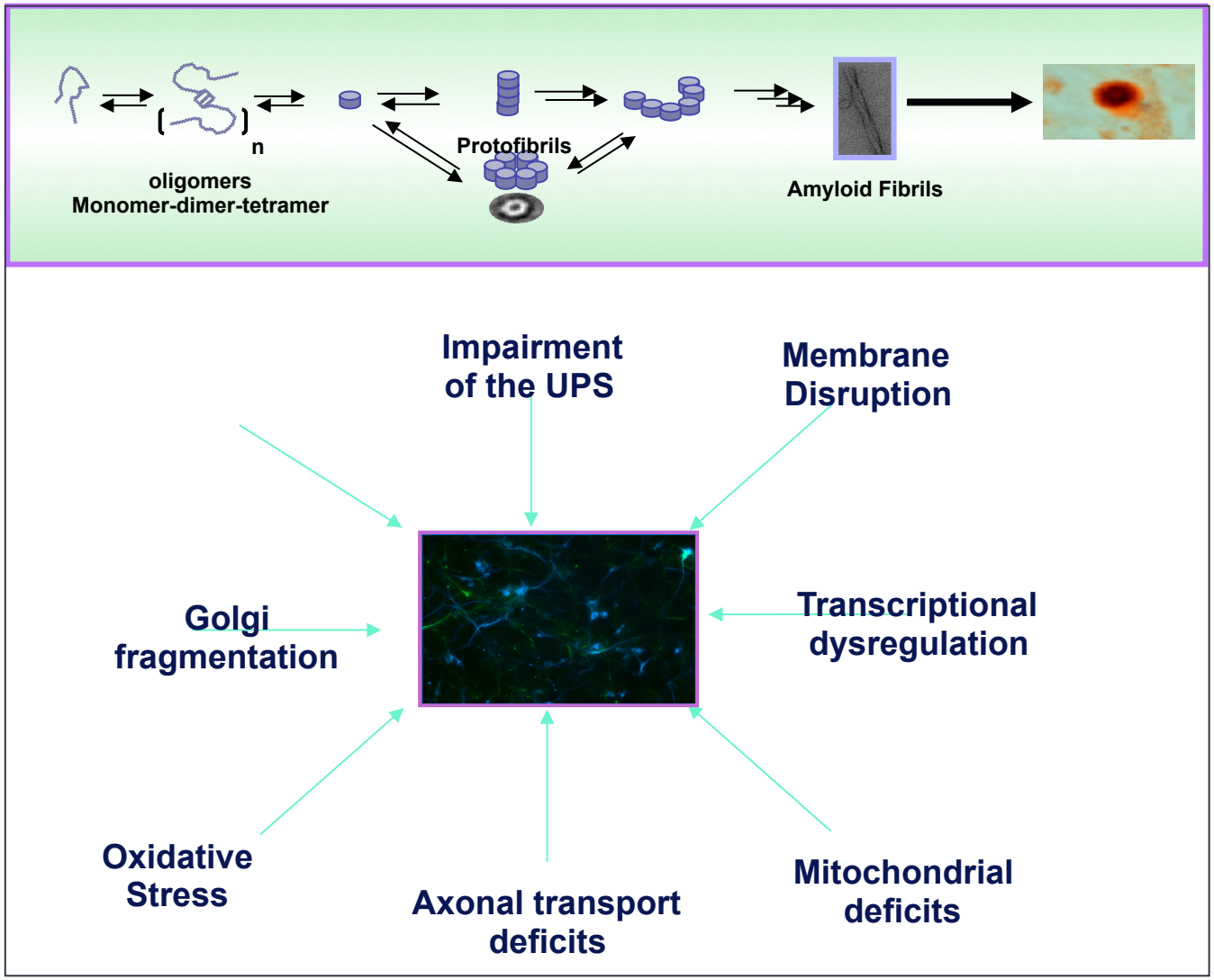


Each image 1 μm x 1 μm

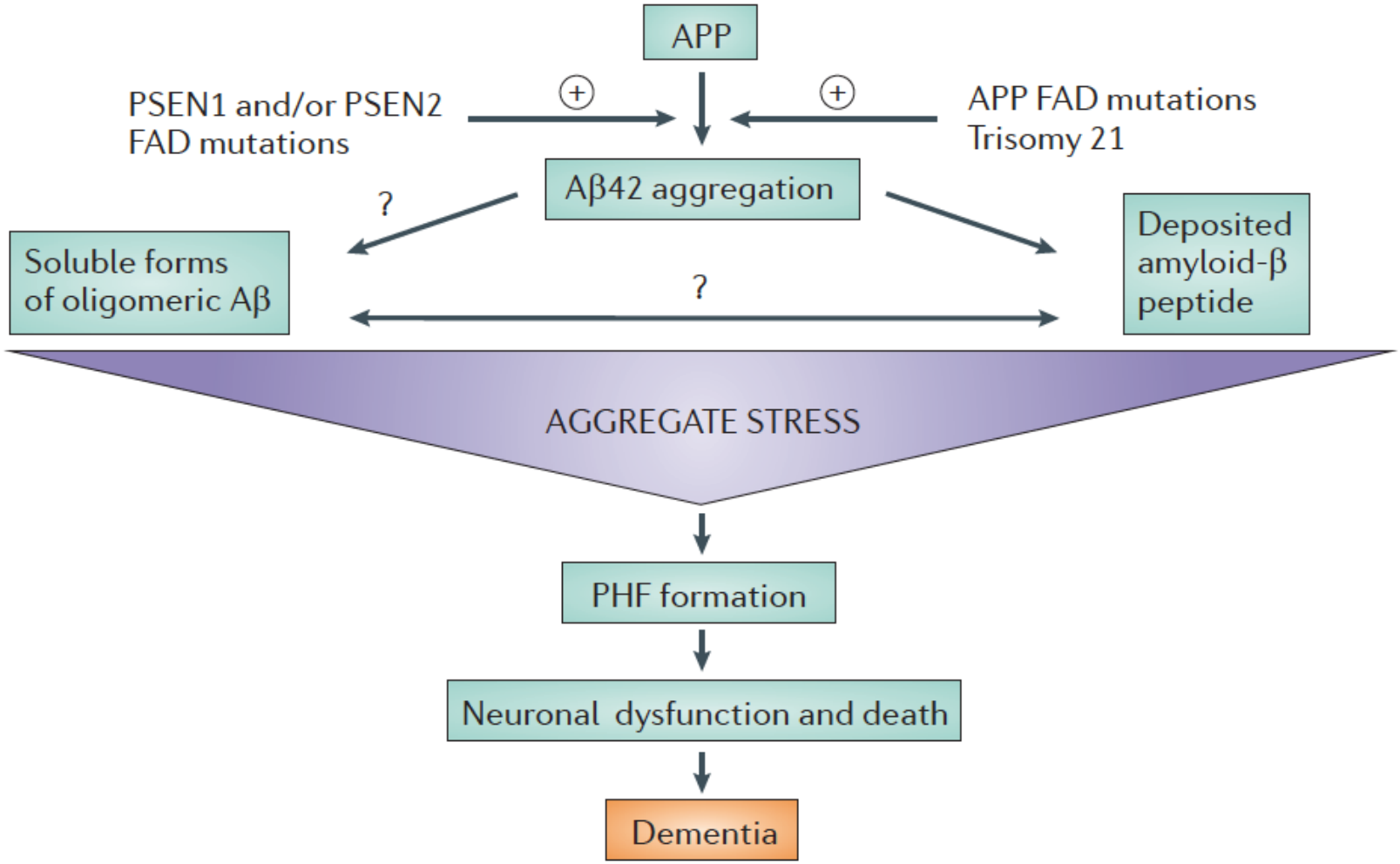
The β-amyloid cascade hypothesis



Mechanisms of Protein Aggregation Induced Toxicity and Neurodgeneration

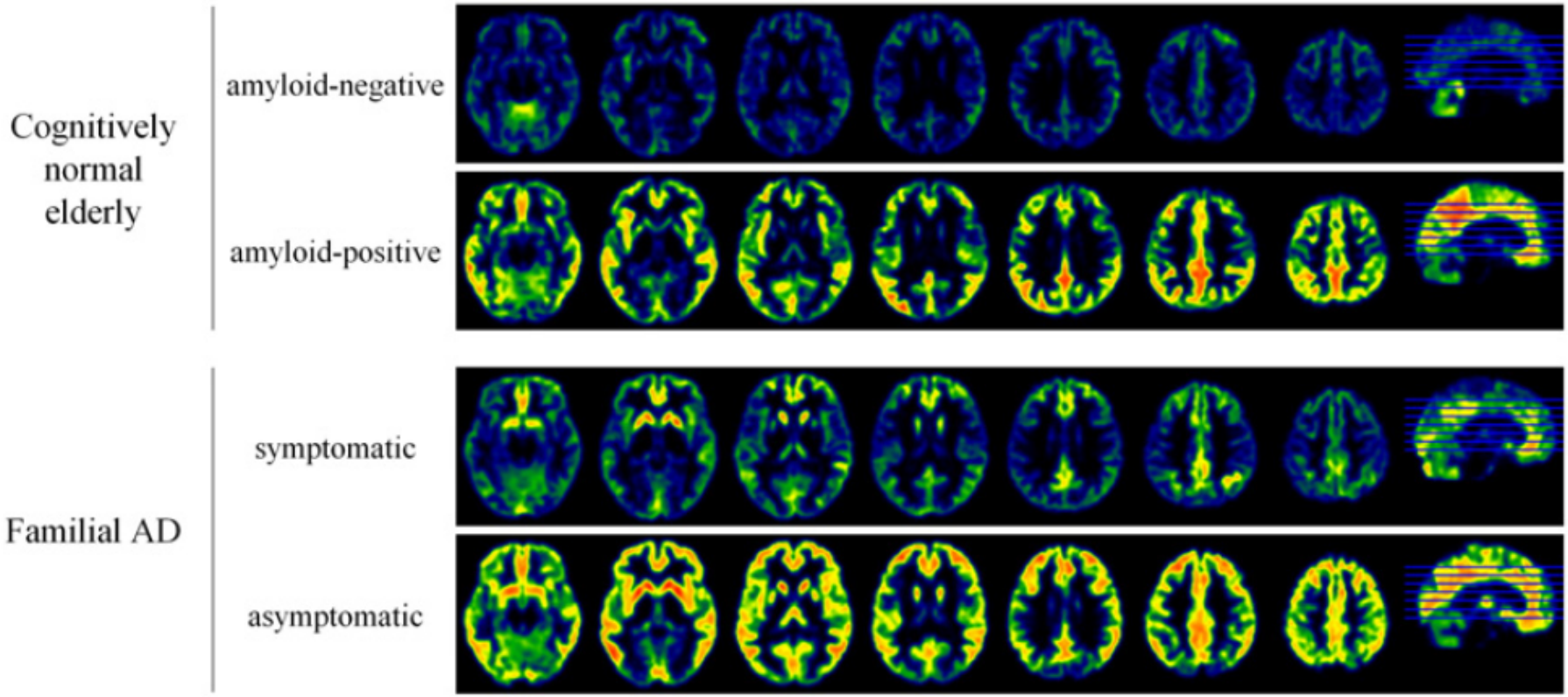


The β-amyloid cascade hypothesis



Validity of β-amyloid cascade hypothesis

- 20-30% of healthy elderly also have amyloid deposits
- Not all (familial) AD cases show amyloid deposits



Alzheimer's Disease – Overview

1 Test your knowledge about Alzheimer's disease

2 **Background: Prevalence and History**

3 Symptomatology

4 Pathophysiological hallmarks

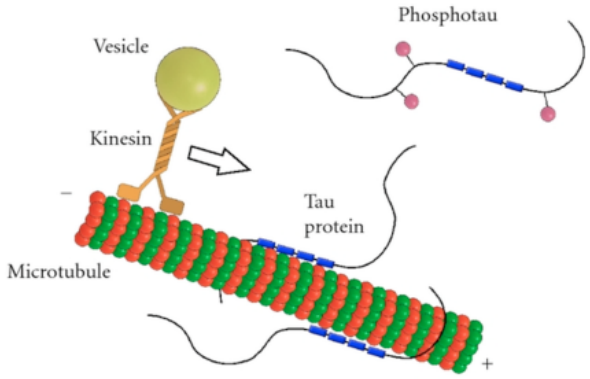
5 **Tau Tangles**

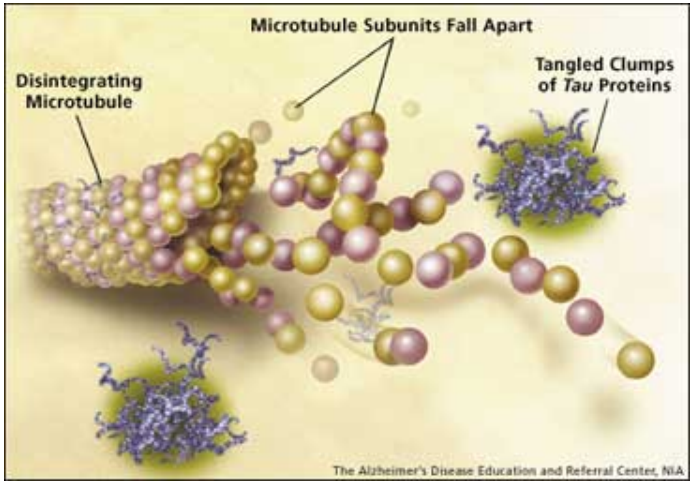
6 Amyloid plaques

7 Risk factors

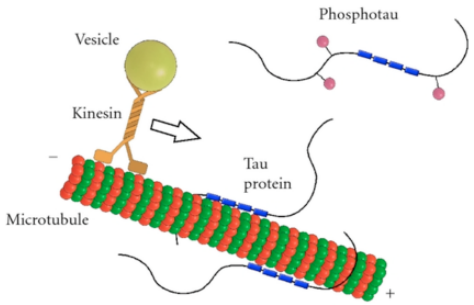
8 Treatment approaches

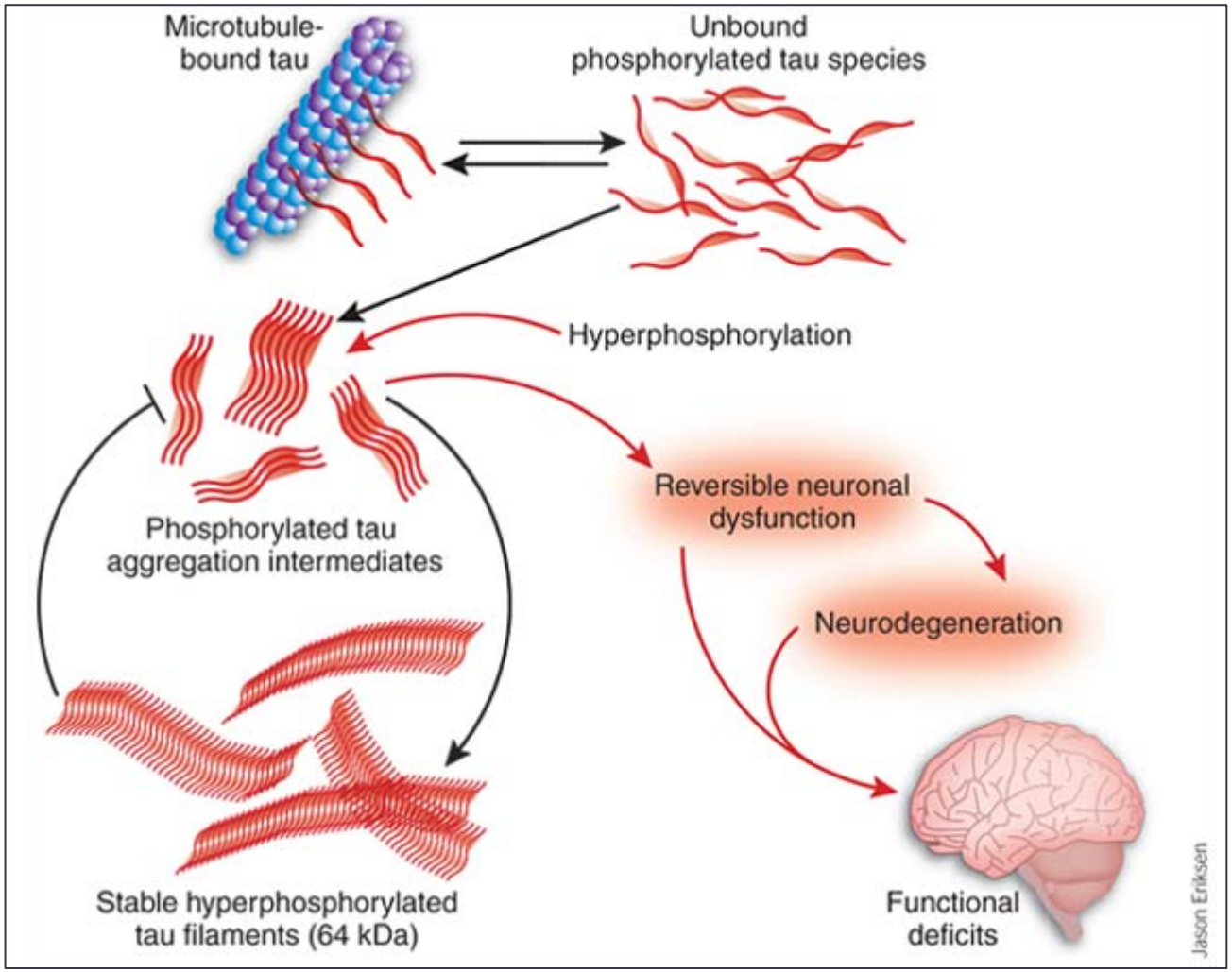
9 Diagnostics and Biomarkers



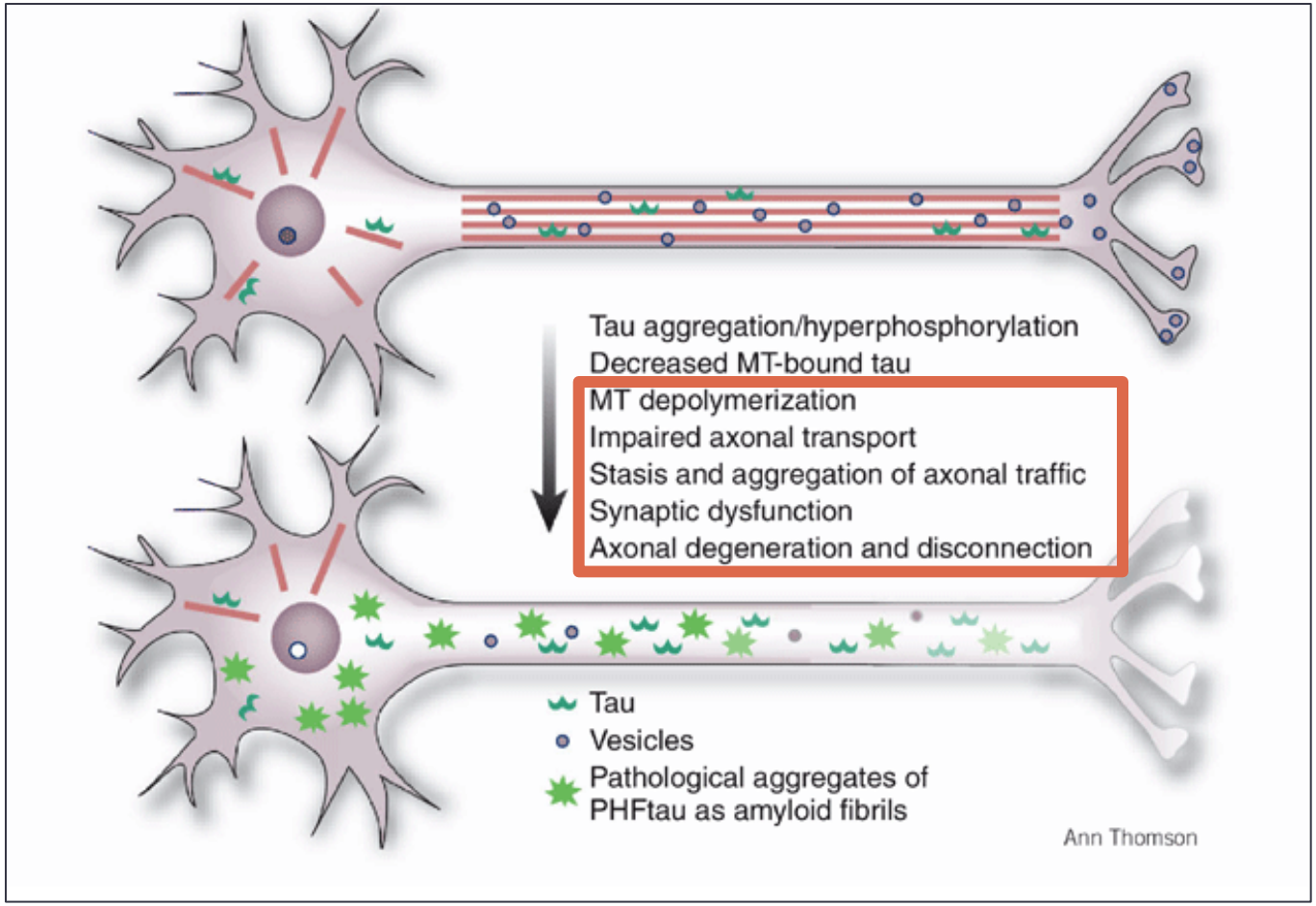


Pathophysiology: Tau Tangles

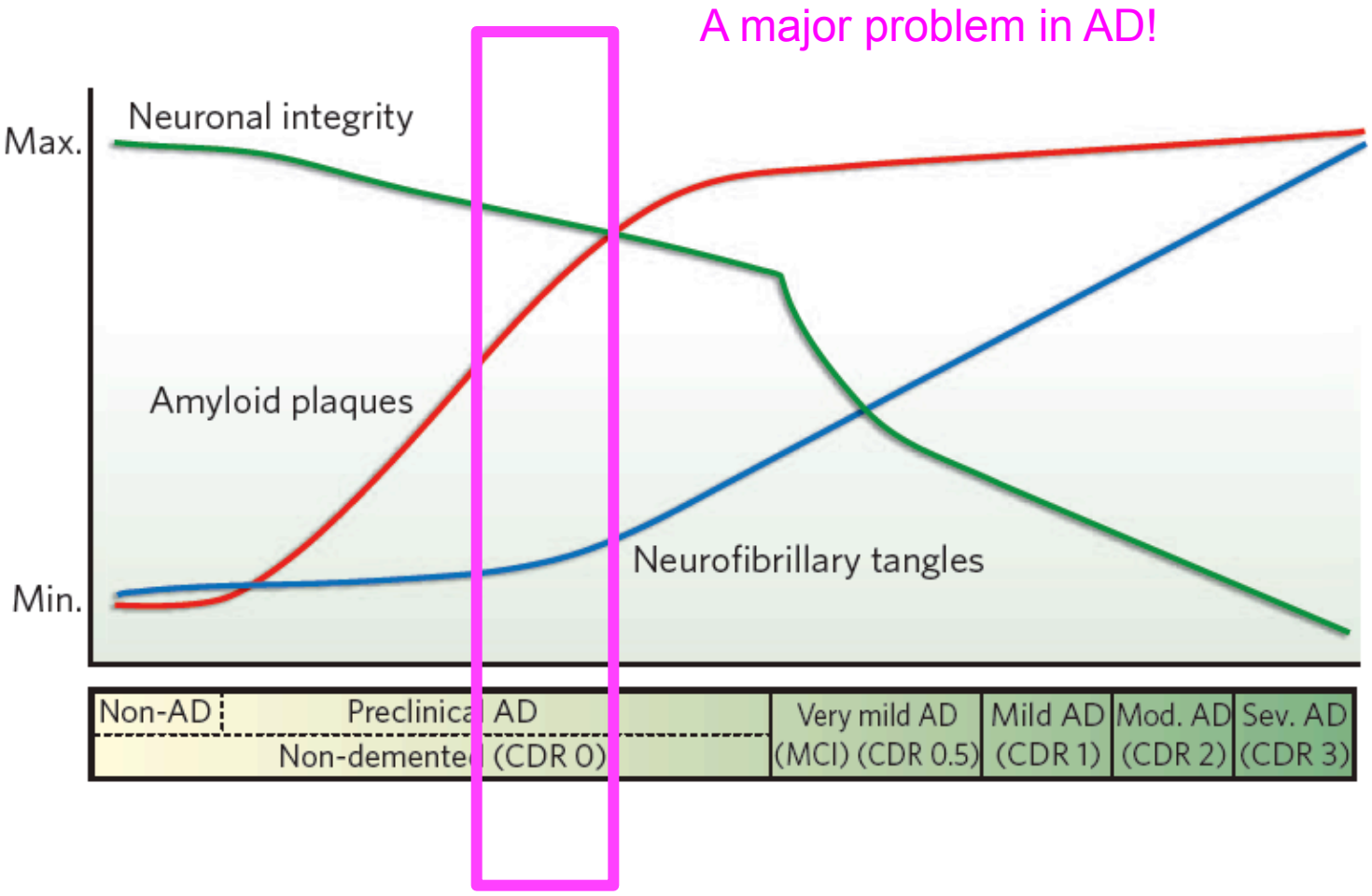




Pathophysiology: Effect of Tau Tangles



Correlation of tangles with AD?



Alzheimer's Disease – Overview

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6 Amyloid plaques

7 **Risk factors**

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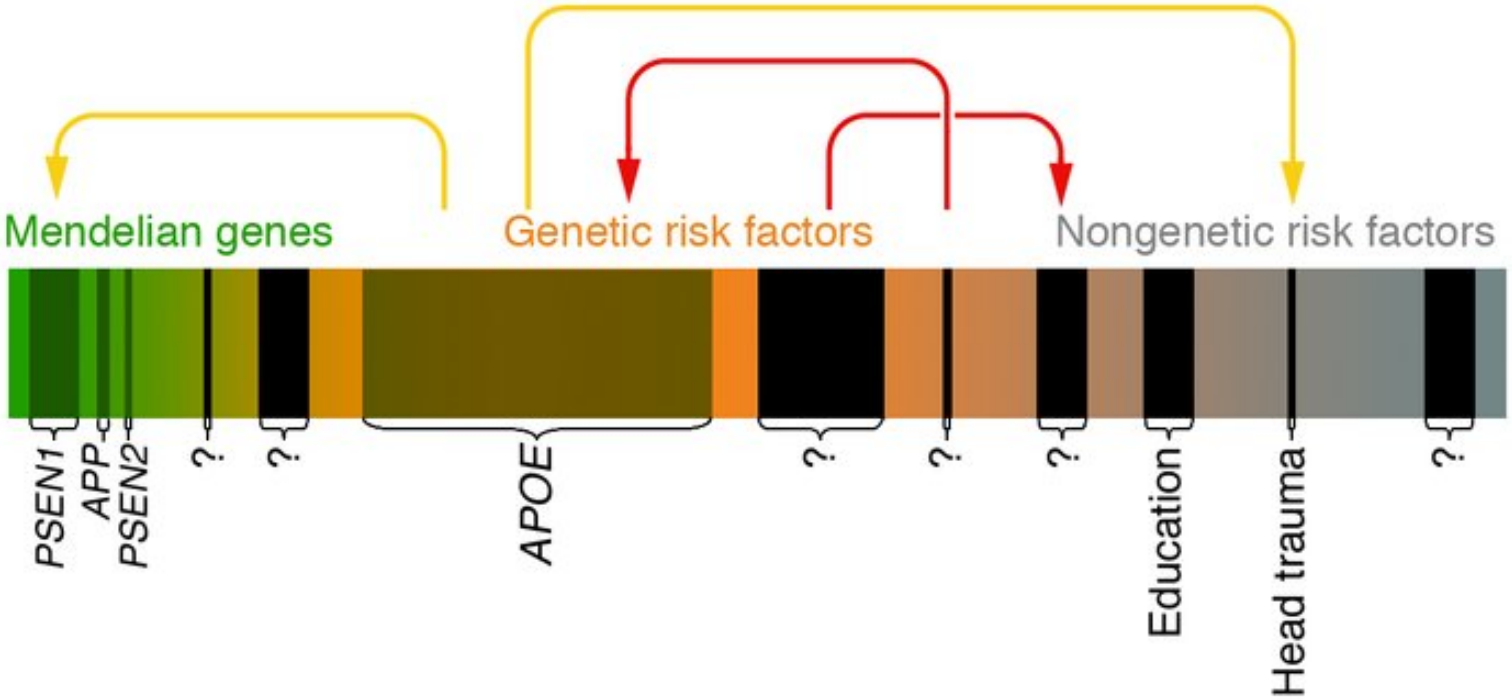
The genetic epidemiology of neurodegenerative disease

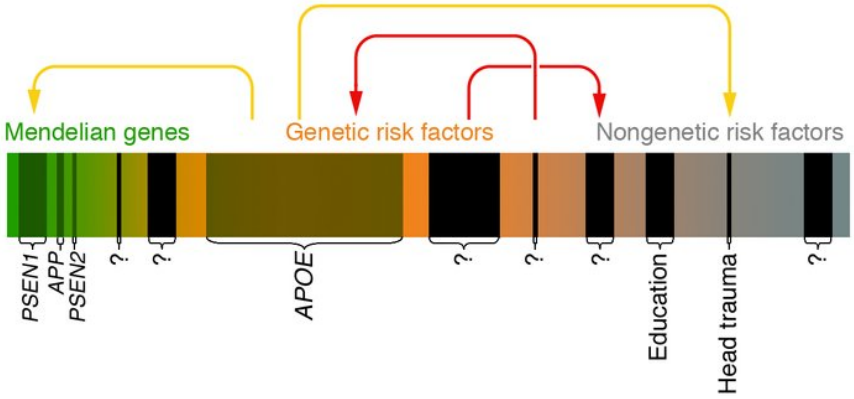
The risk spectrum predisposing to Alzheimer's disease as one continuum



- The width of these boxes approximately represents the relative contribution to the overall risk
- Colored arrows indicate possible gene-gene and gene-environment interaction patterns:

Source: Lars Bertram, Rudolph E. Tanzi, *J Clin Invest.* 2005;115(6):1449-1457. doi:10.1172/JCI24761.

Genetic risk factors for AD



- **Deterministic Genes/Early Onset** :

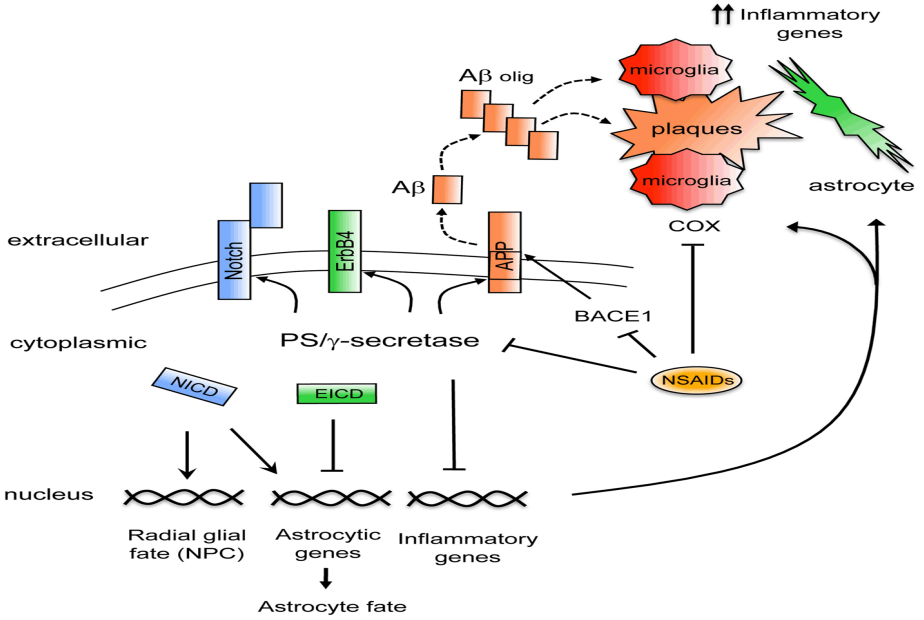
  = Directly cause a disease, guaranteeing that anyone who inherits them will develop the disorder.

- Rare genes that directly cause Alzheimer's in only a few hundred extended families worldwide.
- This type is known as "**Familial Alzheimer's disease**", and many family members in multiple generations are affected.
- **BUT**: True familial AD accounts for **less than 5%** of the cases.

http://www.alz.org

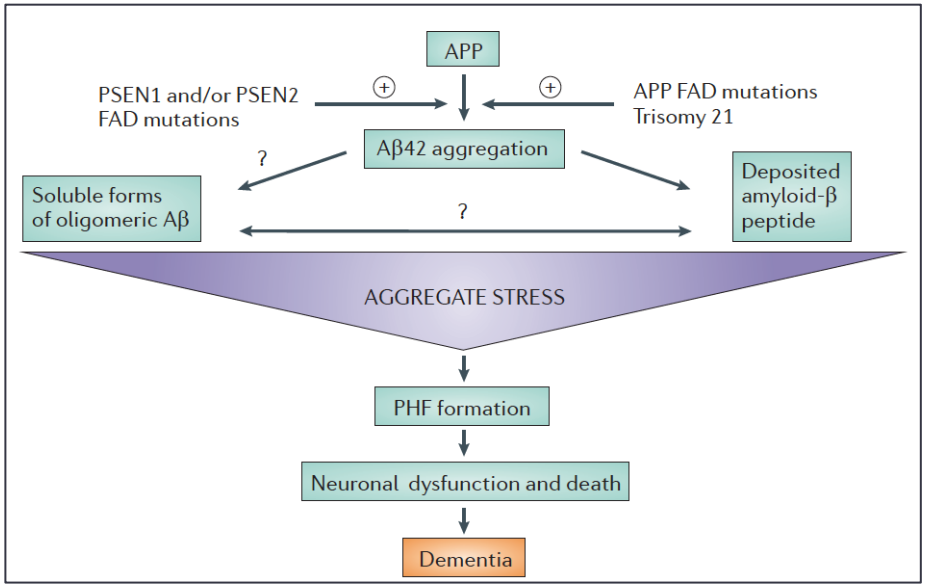
Genetic risk factors for AD

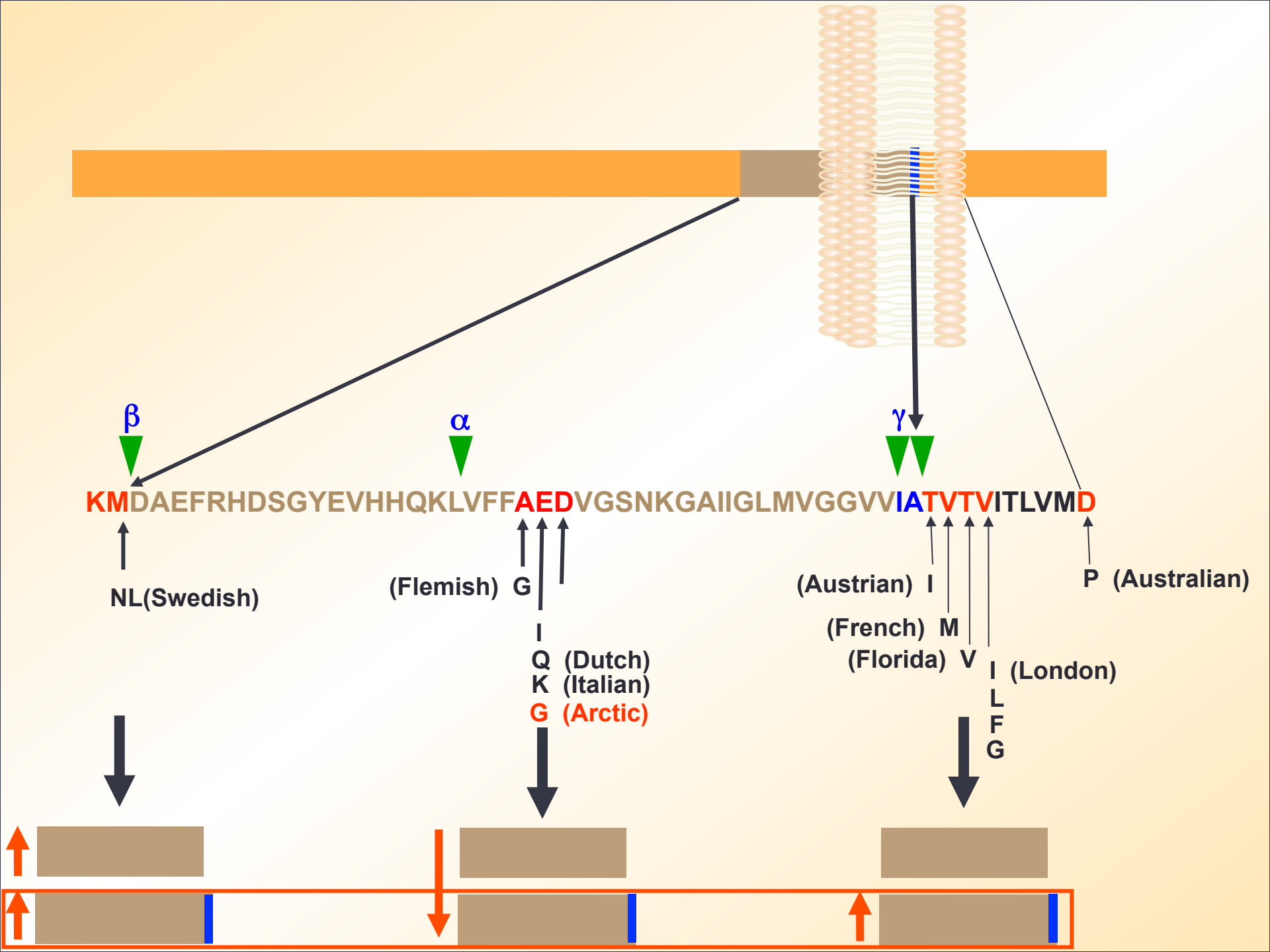
- **Deterministic Genes/Early Onset**:
  - APP FAD mutations
  - Mutations in PSEN1 and/or PSEN2:
    - Code for γ-secretase complex



AD-Mutations

Chromosome 21	Chromosome 14	Chromosome 1
Abnormal **amyloid precursor protein (APP).**	Abnormal **presenilin 1**	Abnormal **presenilin 2**




β
α
γ
KMDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVTVITLVMD
NL(Swedish)
(Flemish) G
I
Q (Dutch)
K (Italian)
G (Arctic)
(Austrian) I
(French) M
(Florida) V
I (London)
L
F
G
P (Australian)

Genetic risk factors for AD

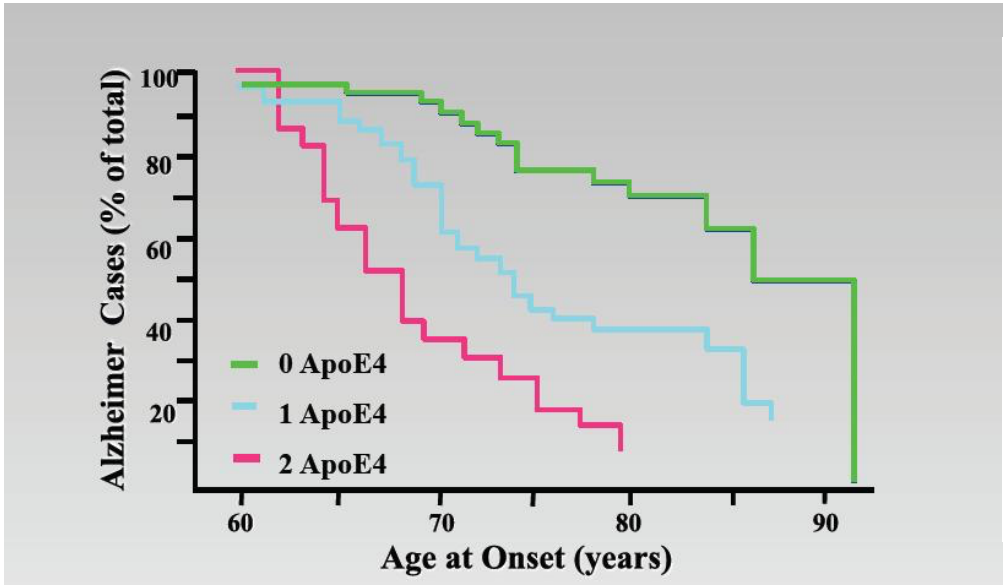
- **Risk Genes**
  - Risk genes increase the likelihood of developing a disease but do not guarantee it will happen.
  - **APOE-e4**

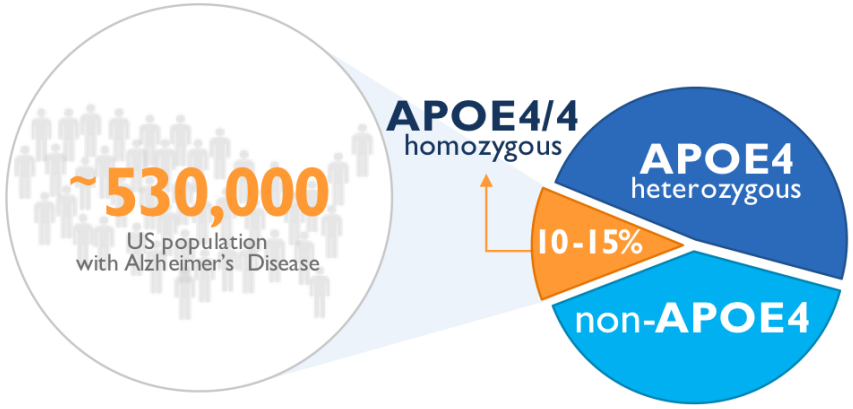
= one of three common forms of the APOE (apolipoprotein) gene.

- Everyone inherits a copy of some form of APOE from each parent.
- Those who inherit one copy of APOE-e4 have an increased risk of developing Alzheimer's.
- Those who inherit two copies have an even higher risk.
- In addition to raising risk, APOE-e4 may tend to make symptoms appear at a younger age than usual.

APOE4 is the strongest genetic risk factor for patients with late-onset Alzheimer's disease

Survival Curve





There are three major isoforms (ApoE2, ApoE3, and ApoE4) in humans.
ApoE is produced predominantly by astrocytes and to some extent microglia
ApoE is also expressed in neurons in response to excitotoxic injury
ApoE plays important role in the transport of HDL-like particles cholesterol and phospho-lipid between cells.

Convergence of genetic risks points to a common disease mechanisms

Amyloid Precursor Protein (APP) – 1987

Presenilin-1 (PS-1)- 1992

Presenilin-2 (PS-2)- 1993

Apolipoprotein E4 (APO-e4) - 1993

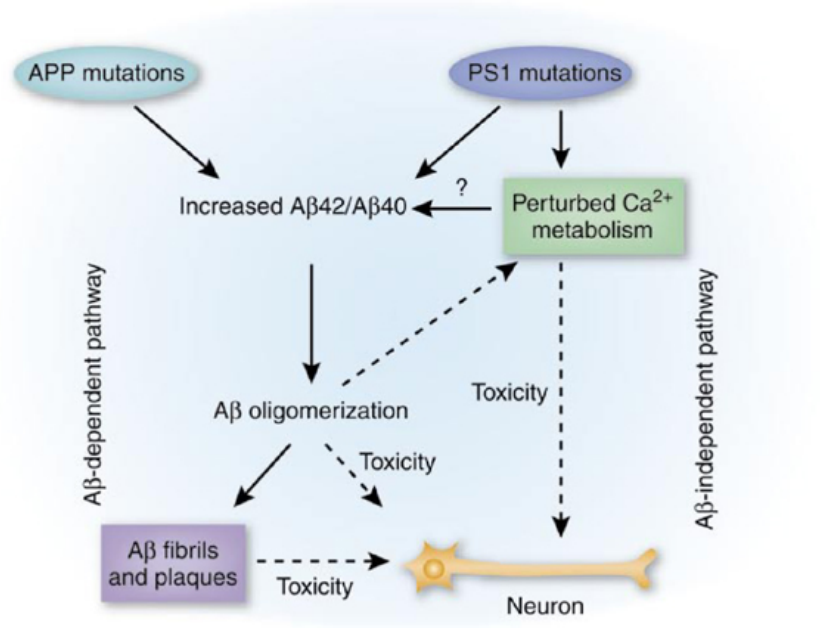
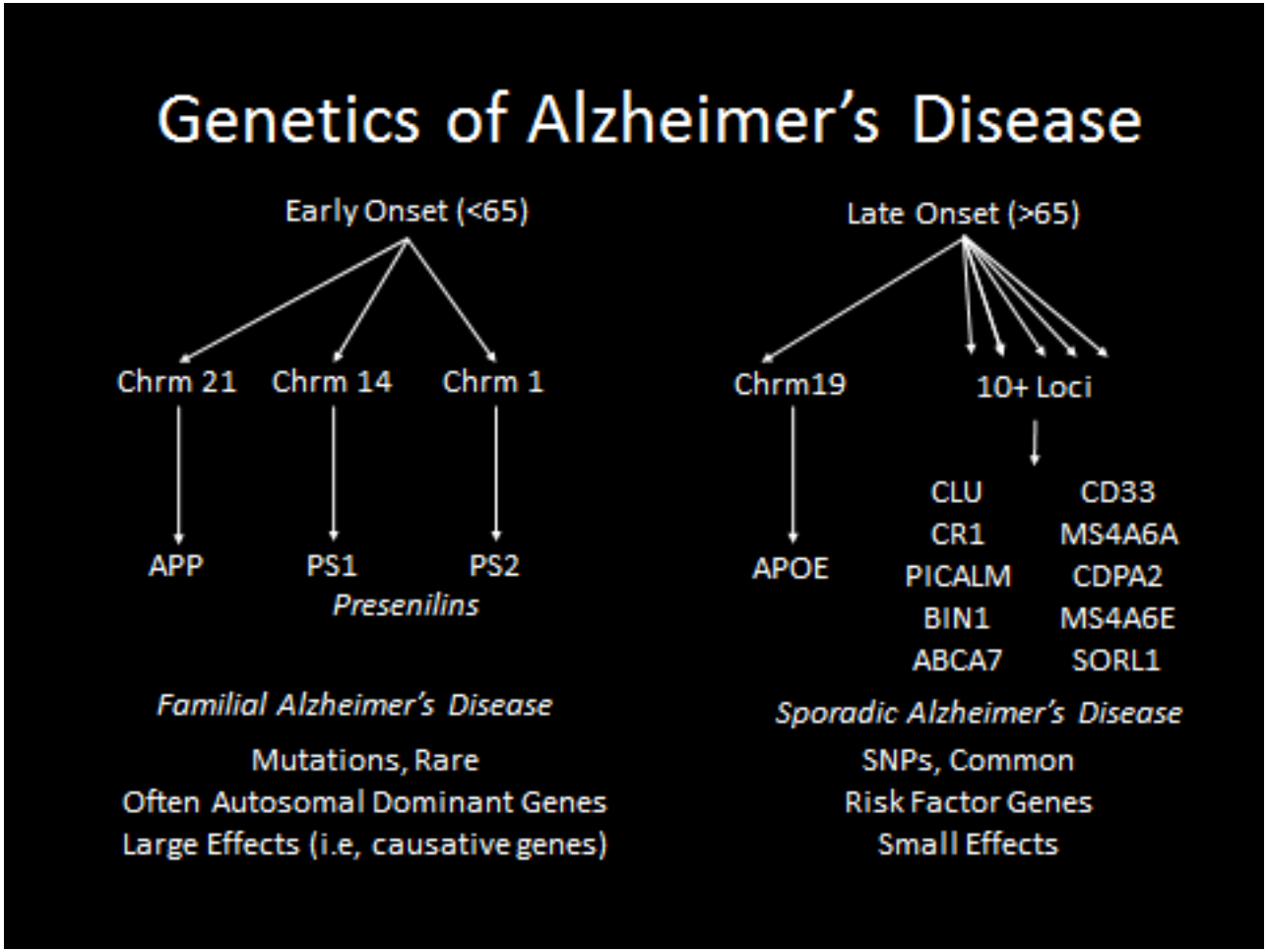


Table 1

Overview of established neurodegenerative disease genes

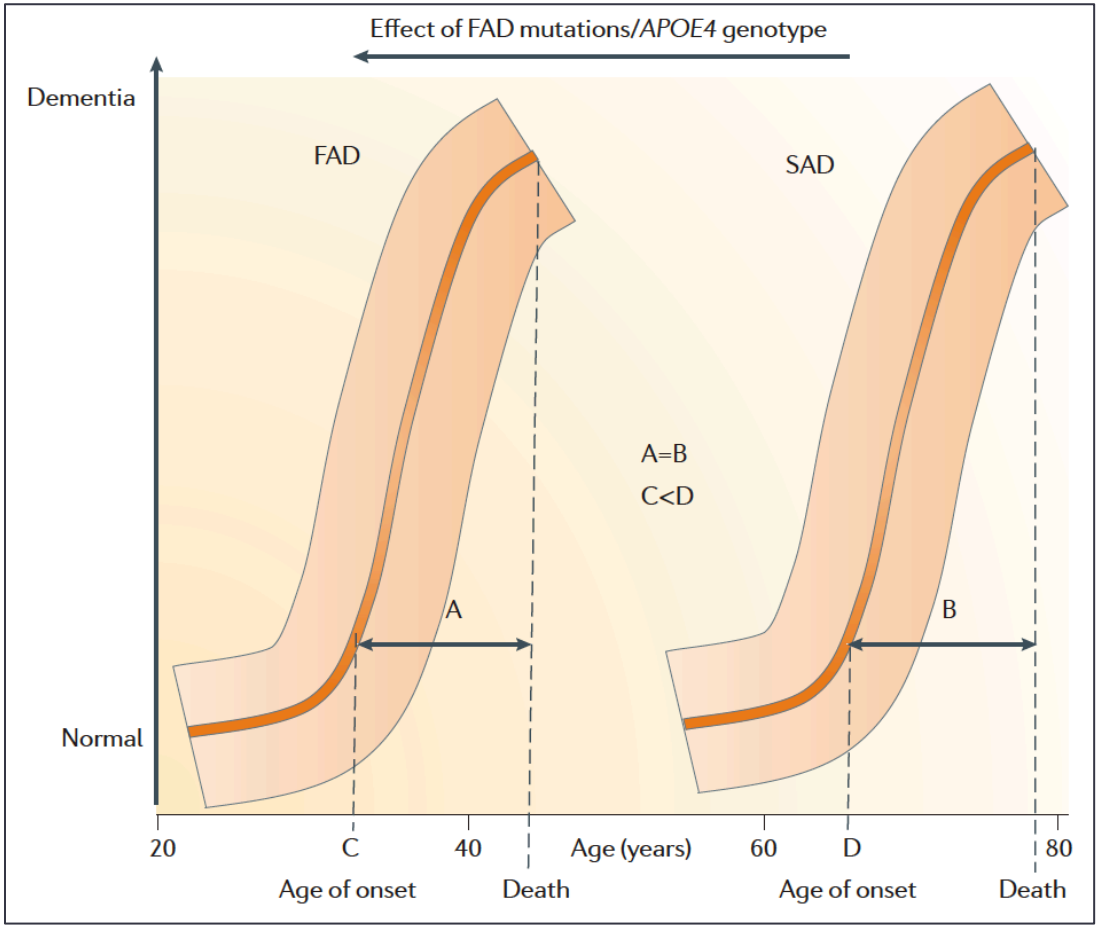
Disease	Gene (first ref.)	Protein	Location	Inheritance	Relevance to pathogenesis
AD	*APP* (15)	Aβ precursor protein	21q21	Dominant	Altered Aβ production ($Aβ_{42}/Aβ_{40}$ ratio ↑) and aggregation
AD	*APOE* (21, 22)	Apolipoprotein E	19q13	Risk factor	Unknown (Aβ aggregation? lipid metabolism?)
AD	*PSEN1* (16)	Presenilin 1	14q24	Dominant	Altered Aβ production ($Aβ_{42}/Aβ_{40}$ ratio ↑)
AD	*PSEN2* (17, 18)	Presenilin 2	1q31	Dominant	Altered Aβ production ($Aβ_{42}/Aβ_{40}$ ratio ↑)

Familial vs sporadic AD



Genetic risk factors for AD: A case of sporadic AD

Familial AD (FAD)



Sporadic AD (FAD)

Familial Alzheimer's disease (FAD) mutations and the apolipoprotein E4 (*APOE4*) genotype is to decrease the age of onset of the disease, with little evidence for an effect on disease duration.

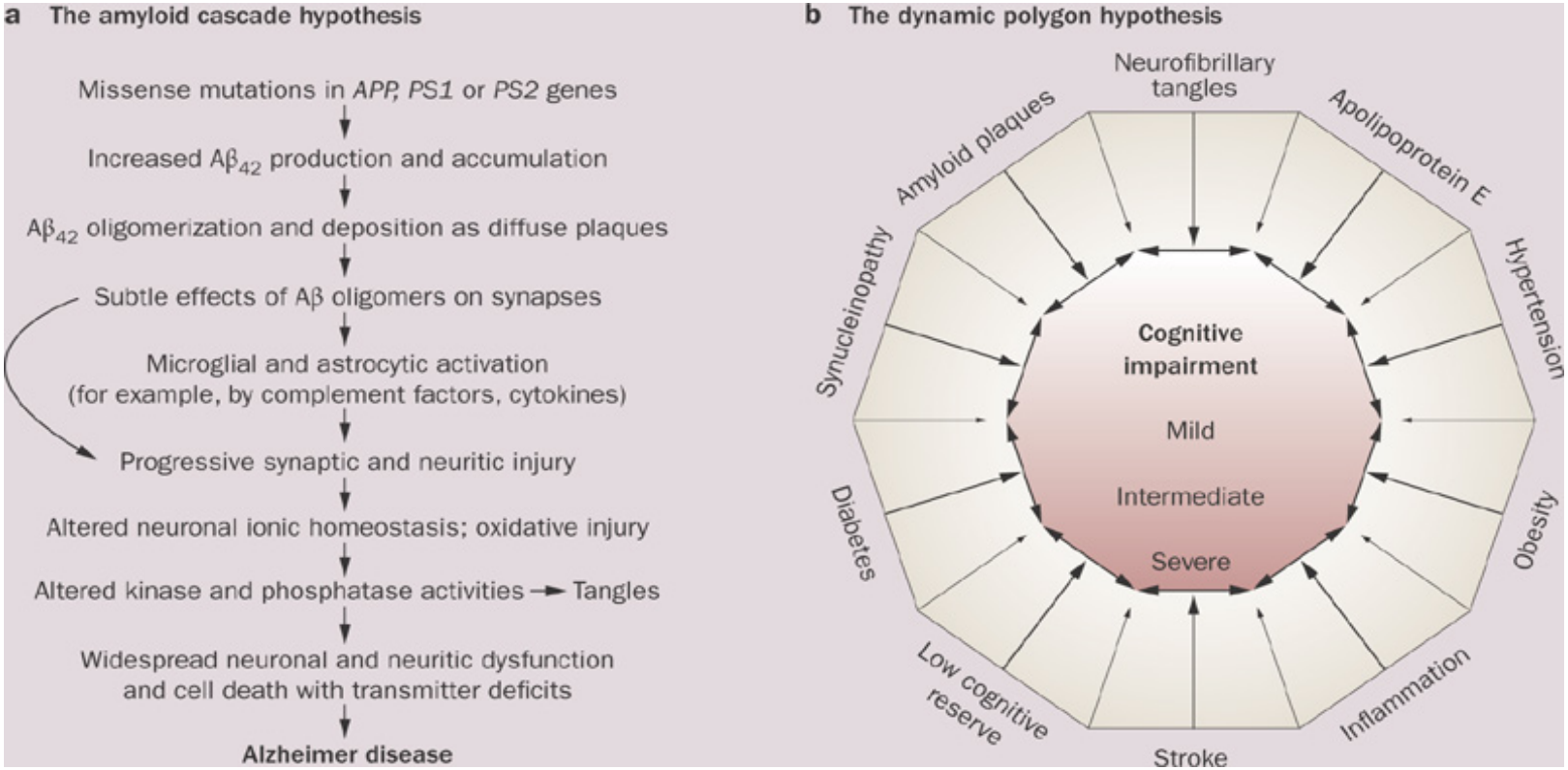
Nature Reviews Drug Discovery **10**, 698-712

Risk factors for AD

- Age
- Carrying a risk gene (APOE4 and others)
- Others:
  - Diabetes mellitus
  - Midlife hypertension
  - Midlife obesity
  - Midlife inactivity
  - Depression
  - Smoking
  - Low educational attainment

Risk factors for AD

- The dynamic polygon hypothesis:



- Early-onset dementia results from toxicity associated with aggregation of plaques and tangles (although not necessarily in a linear fashion)
- Late-life dementia, on the other hand, is considered to be a more complex disease
- In this model, plaques and tangles are two components among a larger set of factors that modulate synaptic density and the size of the cortex and hippocampus, cognition and quality of life.

Fotuhi et al., *Nature Reviews Neurology* 5, 649-658 (2009)

Let’s see how much you can remember

How many of these young women, shown here in their 20s during World War II, might have Alzheimer's disease today?

A) 1

B) 2

C) 3

Alzheimer's disease is considered a terminal illness.

- True
- False

Alzheimer's disease can be diagnosed by a blood test.

- True
- False

When can a definite diagnosis of Alzheimer's disease be made?

A) At the onset of AD
B) After death of the patient
C) When all signs and symptoms are present
D) At the first sign of dementia

How often can Alzheimer's be accurately diagnosed?

A) 10 percent of the time
B) 50 percent of the time
C) 90 percent of the time
D) Almost never

Alzheimer's disease can be cured if detected early

- True
- False

Which is the primary trigger AD pathology?

- Amyloid Plaques
- Neurofibrillary Tangles
- Both

Which of the following pathways leads to production of amyloid-beta, amyloidogenic pathway?

- Sequential APP cleavage by α and γ secretases
- Sequential APP cleavage by α and β secretases
- Cleavage by γ secretases

Alzheimer's disease can resemble the early stages of

A) Schizophrenia
B) Parkinson’s disease
C) Multiple Sclerosis
D) Down Syndrome

Sleep deprivation increase the risk of developing Alzheimer's disease

- True
- False

Sleep deprivation is sufficient to increase Amyloid-β levels and accumulation and may increase the risk of AD

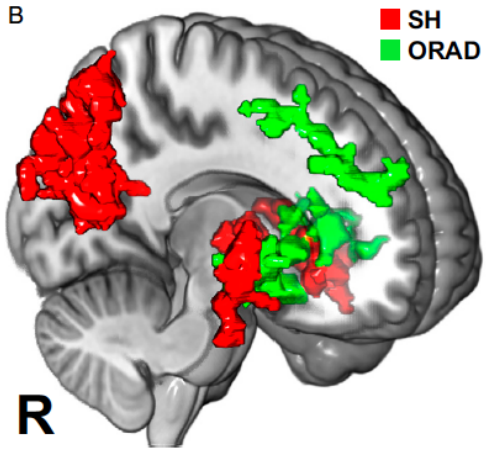
PNAS

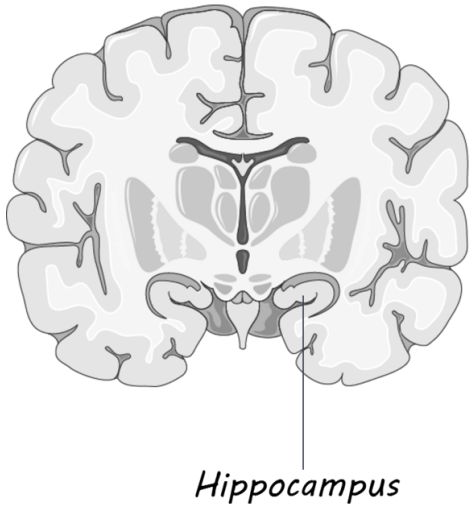
β-Amyloid accumulation in the human brain after one night of sleep deprivation

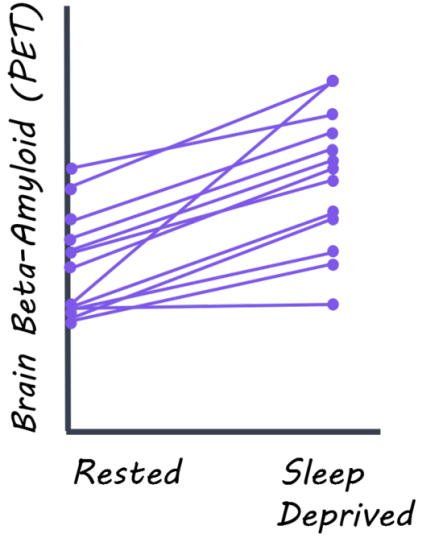
Ehsan Shokri-Kojori[a,1], Gene-Jack Wang[a,1], Corinde E. Wiers[a], Sukru B. Demiral[a], Min Guo[a], Sung Won Kim[a], Elsa Lindgren[a], Veronica Ramirez[a], Amna Zehra[a], Clara Freeman[a], Gregg Miller[a], Peter Manza[a], Tansha Srivastava[a], Susan De Santi[b], Dardo Tomasi[a], Helene Benveniste[c], and Nora D. Volkow[a,1]

[a]Laboratory of Neuroimaging, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892; [b]Piramal Pharma Inc., Boston, MA 02108; and [c]Department of Anesthesiology, Yale School of Medicine, New Haven, CT 06510

Edited by Michael E. Phelps, University of California, Los Angeles, CA, and approved March 13, 2018 (received for review December 14, 2017)







Parameters assessed: Amyloid load and Mood

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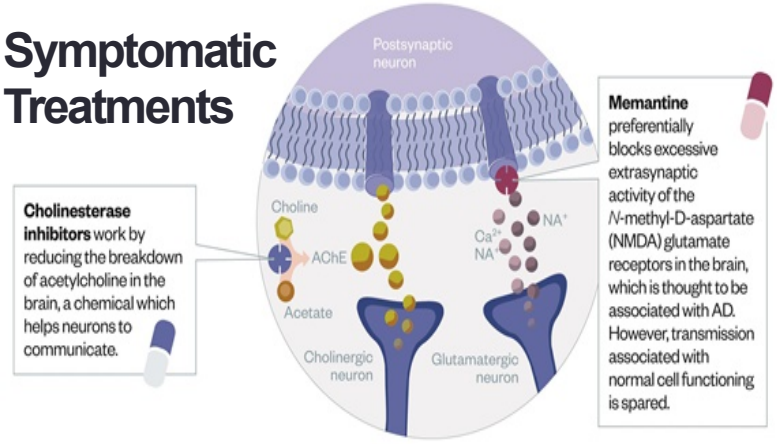
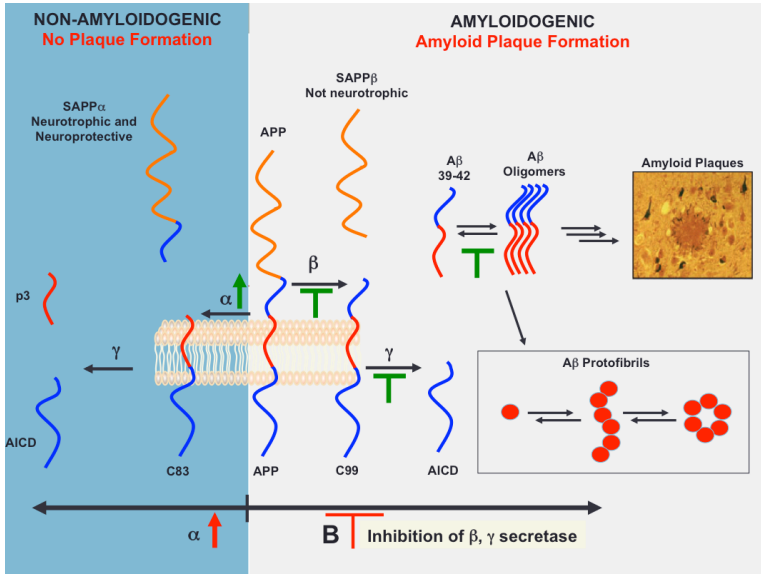
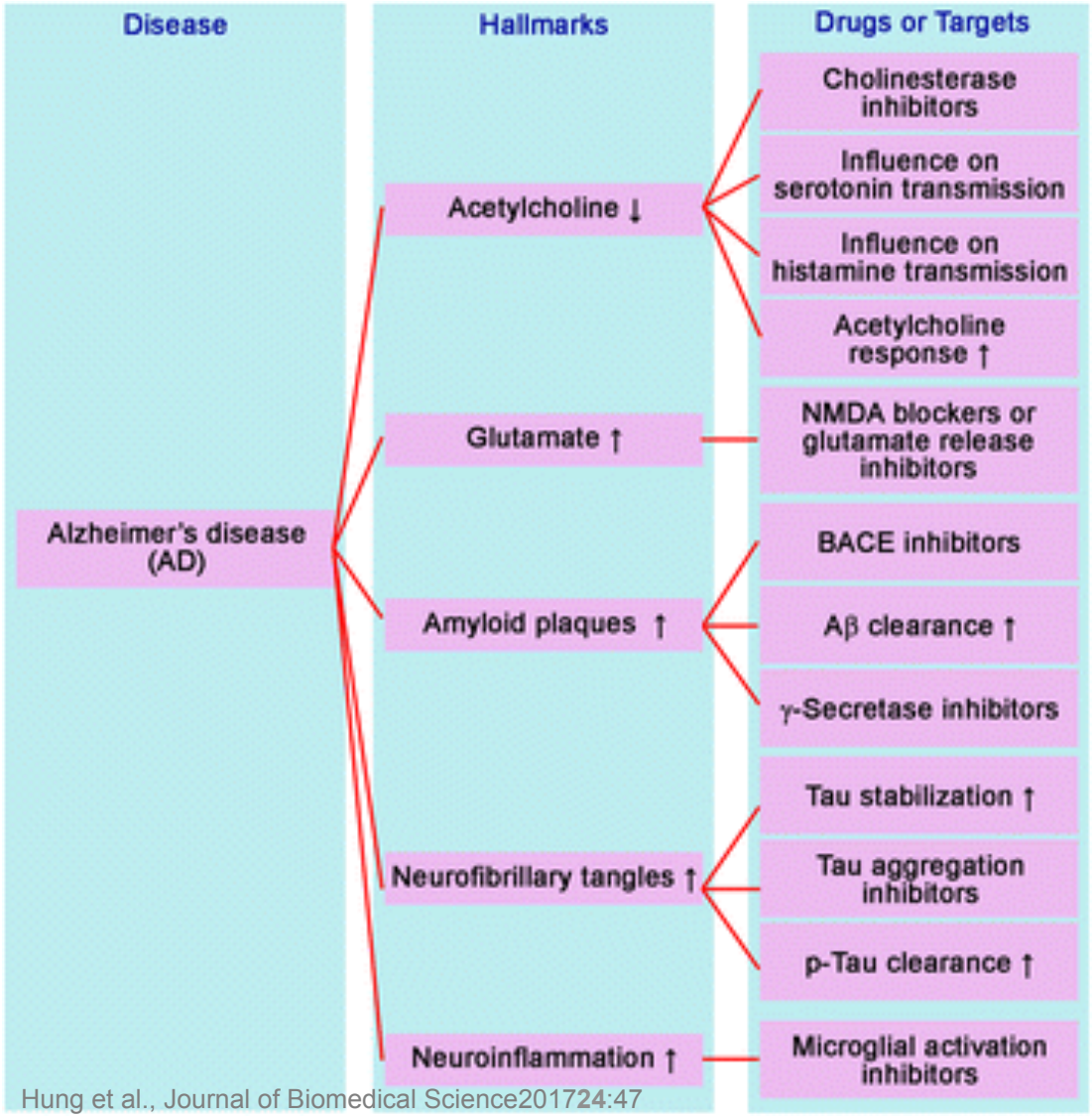
Therapeutic targets in the treatment of Alzheimer's disease according to neuropathological hallmarks

Symptomatic Treatments



Disease Modifying Treatments

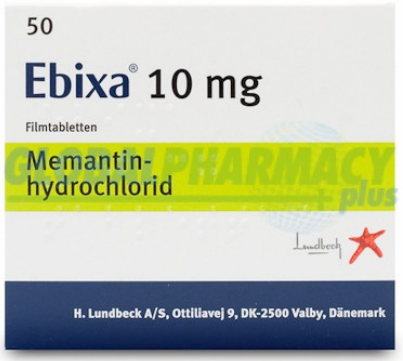




Hung et al., Journal of Biomedical Science2017**24**:47

Treatment approaches for AD:

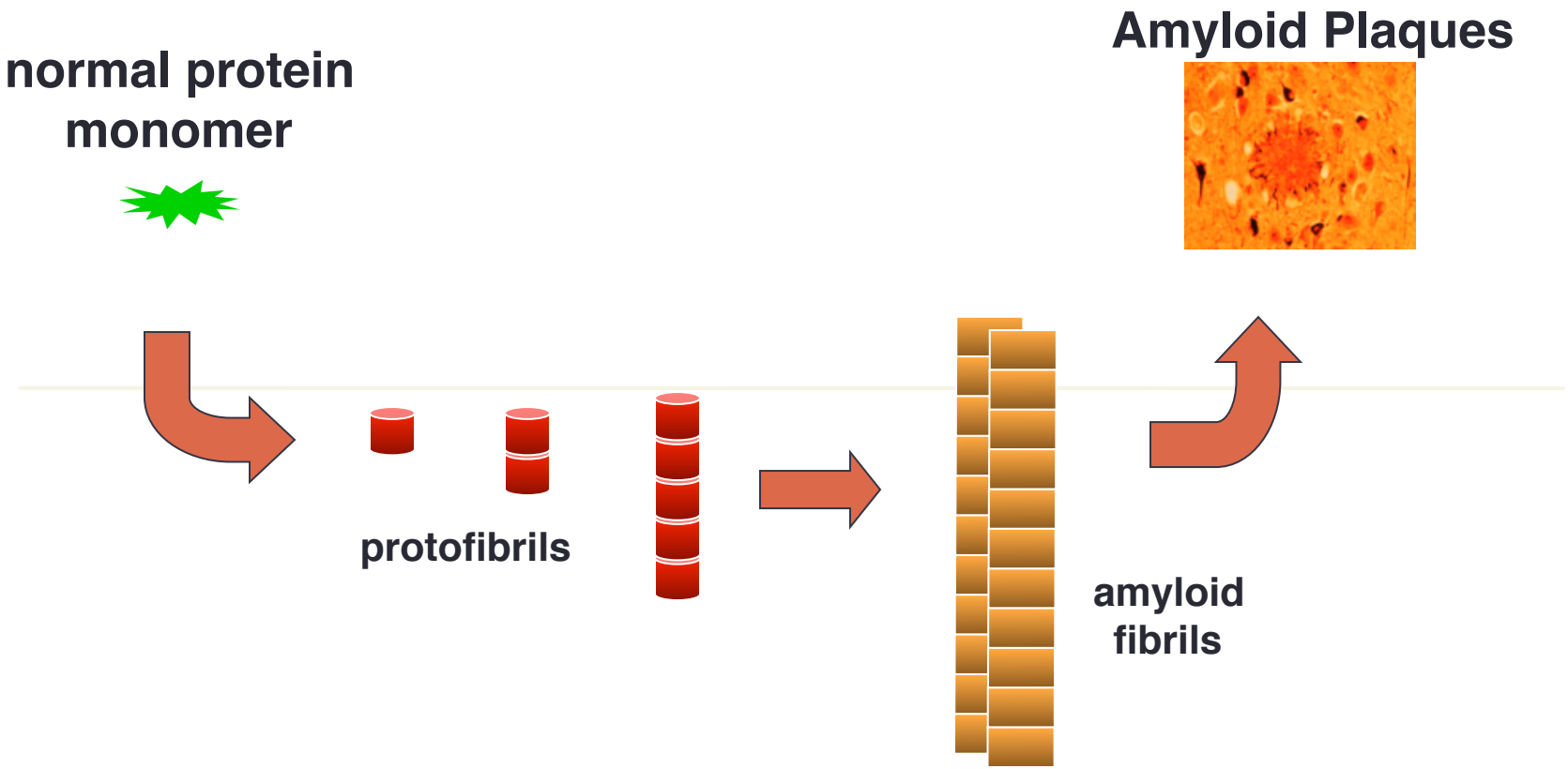
- 2 types of FDA approved drugs against cognitive symptoms
  - **Cholinesterase inhibitors**
    - Prevent the breakdown of acetylcholine, a chemical messenger important for learning and memory.
      - Donepezil (Aricept)
      - Rivastigmine (Exelon)
      - Galantamine (Razadyne)
      - Tacrine (Cognex)



  - **NMDA receptor antagonist:**
    - Maintenance of glutamatergic synaptic transmission, thereby increasing learning and memory capacities
      - Memantine (Ebixa)

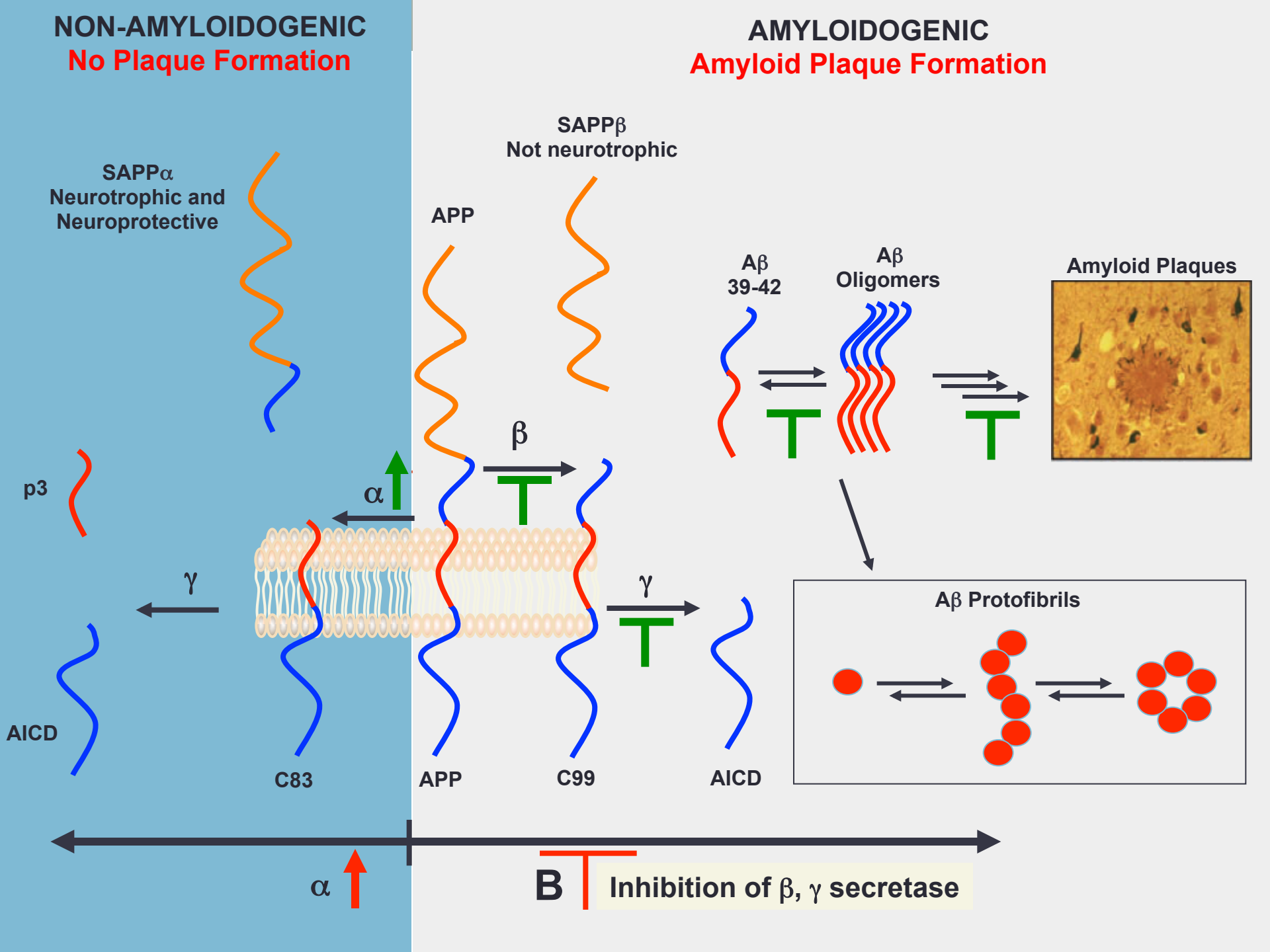
Question 1

Studies on Aβ aggregation plays a central role in the pathogenesis of Alzheimer's disease. **Propose different strategies for the treatment of AD based on targeting this pathway**.

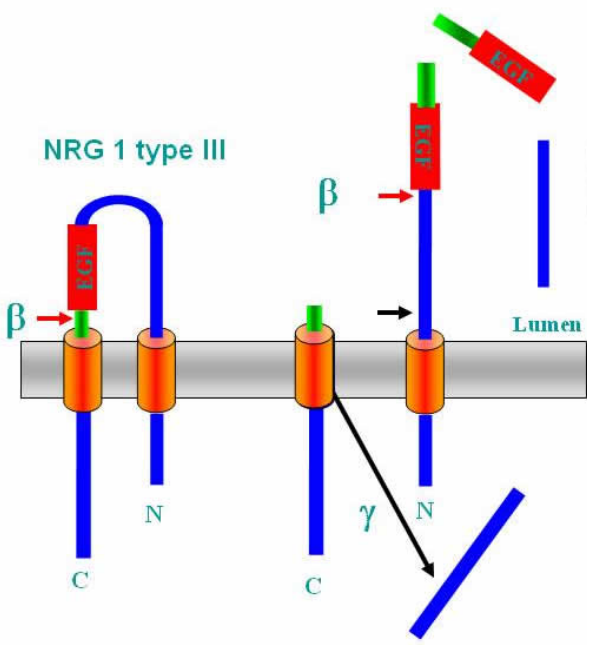


Aβ pathway and the amyloid hypothesis in Alzheimer's disease

- **Inhibition of Aβ production by β-secretase (BACE) inhibitors**
- **Inhibition of Aβ production by γ-secretase inhibitors or modulators**
- **Enhancement of Aβ clearance by active immunotherapy**
- **Enhancement of Aβ clearance by Aβ degrading enzymes**
- **Inhibition of Aβ aggregation and toxicity**


NON-AMYLOIDOGENIC
No Plaque Formation
AMYLOIDOGENIC
Amyloid Plaque Formation
SAPPα
Neurotrophic and
Neuroprotective
SAPPβ
Not neurotrophic
APP
Aβ
39-42
Aβ
Oligomers
Amyloid Plaques
β
α
p3
γ
γ
AICD
C83
APP
C99
AICD
Aβ Protofibrils
α
B
Inhibition of β, γ secretase

Inhibition of β secretase



Highlights

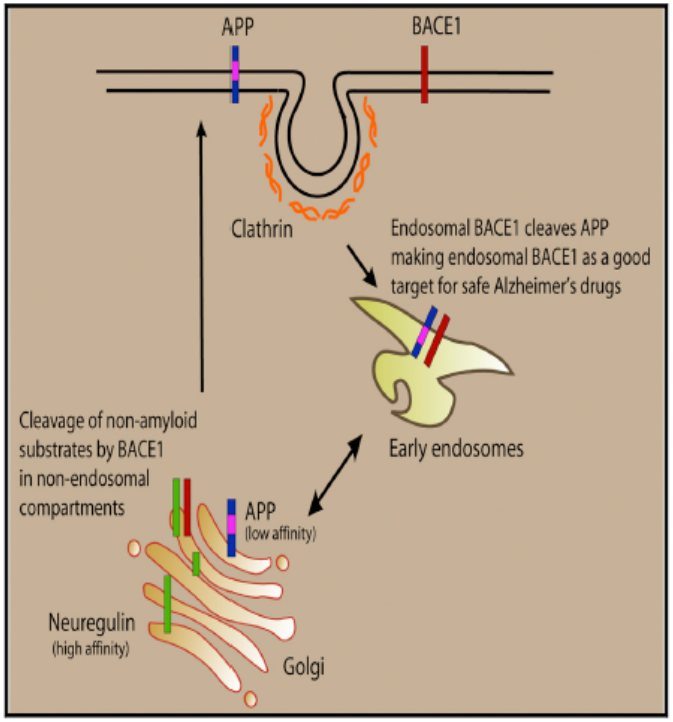
- The AD-linked protease BACE1 cleaves APP to produce toxic β-amyloid peptides
- BACE1 also cleaves the non-amyloid substrates NRG1 and L1
- BACE1 cleavage of NRG1 and L1 is endocytosis-independent, unlike the cleavage of APP
- The endosomally targeted BACE1 inhibitor spares NRG1 and L1 but inhibits APP processing

Article

Cell Reports

Specific Inhibition of β-Secretase Processing of the Alzheimer Disease Amyloid Precursor Protein

Graphical Abstract



Authors

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K. Muruga Poopathi Raja, ...,
Christian Haass, Amedeo Caflisch,
Lawrence Rajendran

Correspondence

rajendran@bli.uzh.ch

In Brief

Ben Halima et al. demonstrate the feasibility of designing drugs targeting the Alzheimer-related enzyme BACE1 without affecting its physiological function. Using structural, biochemical, and cellular approaches, they show that BACE1 inhibitors can be designed to specifically inhibit its disease-causing activity, enhancing their potential as therapeutics without undesired side effects.

Inhibition of BACE1 alters maintenance of muscle spindles and impairs synaptic functions

Inhibition of γ secretase

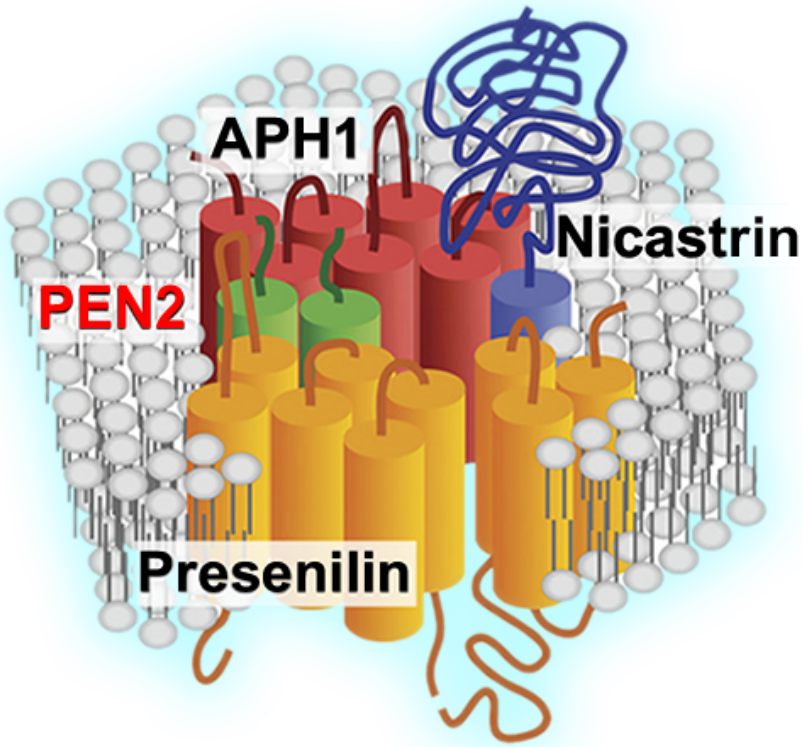
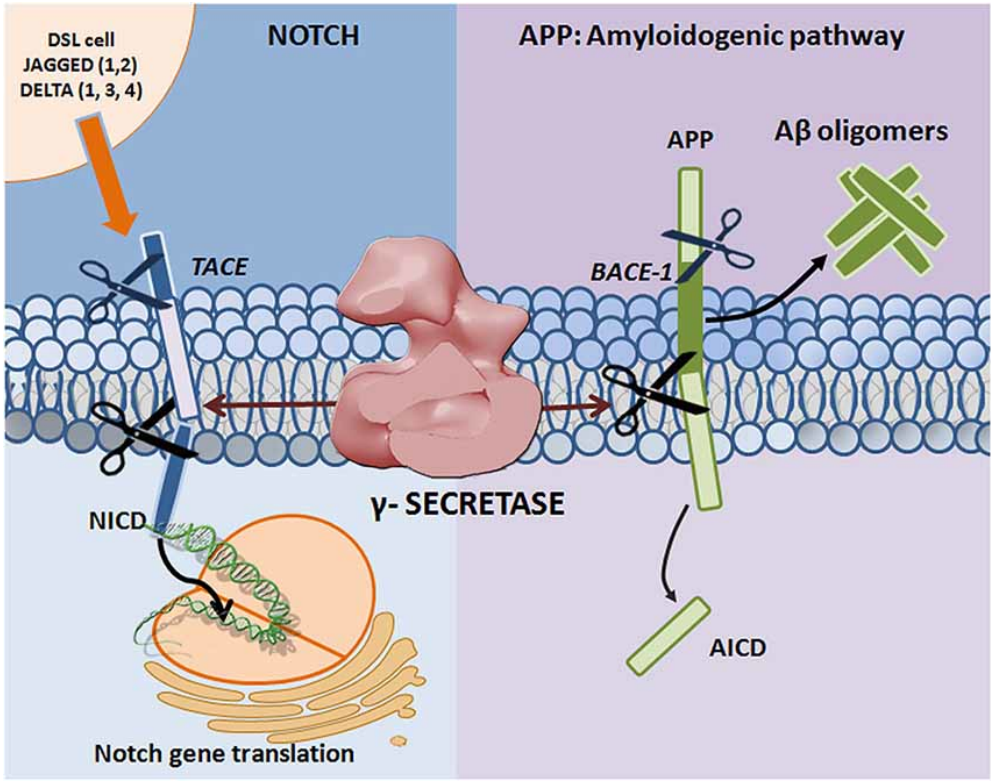


Figure 2 - Gamma-Secretase Complex (Parks. 2007)

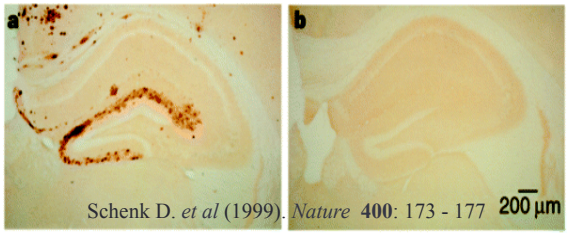


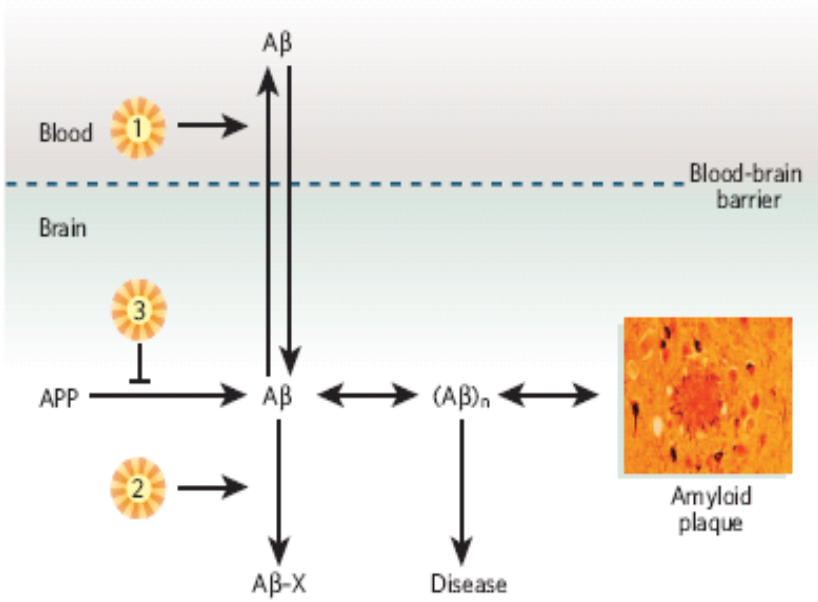
Proteolytic processing of APP and Notch.

Clinical trials of treatments based on reducing Aβ levels and aggregation in AD

1- Modulating APP processing and Aβ levels
   I- NSAIDs
   II- Secretase Inhibitors

2- Aβ vaccine *(Elan/Wyeth)*

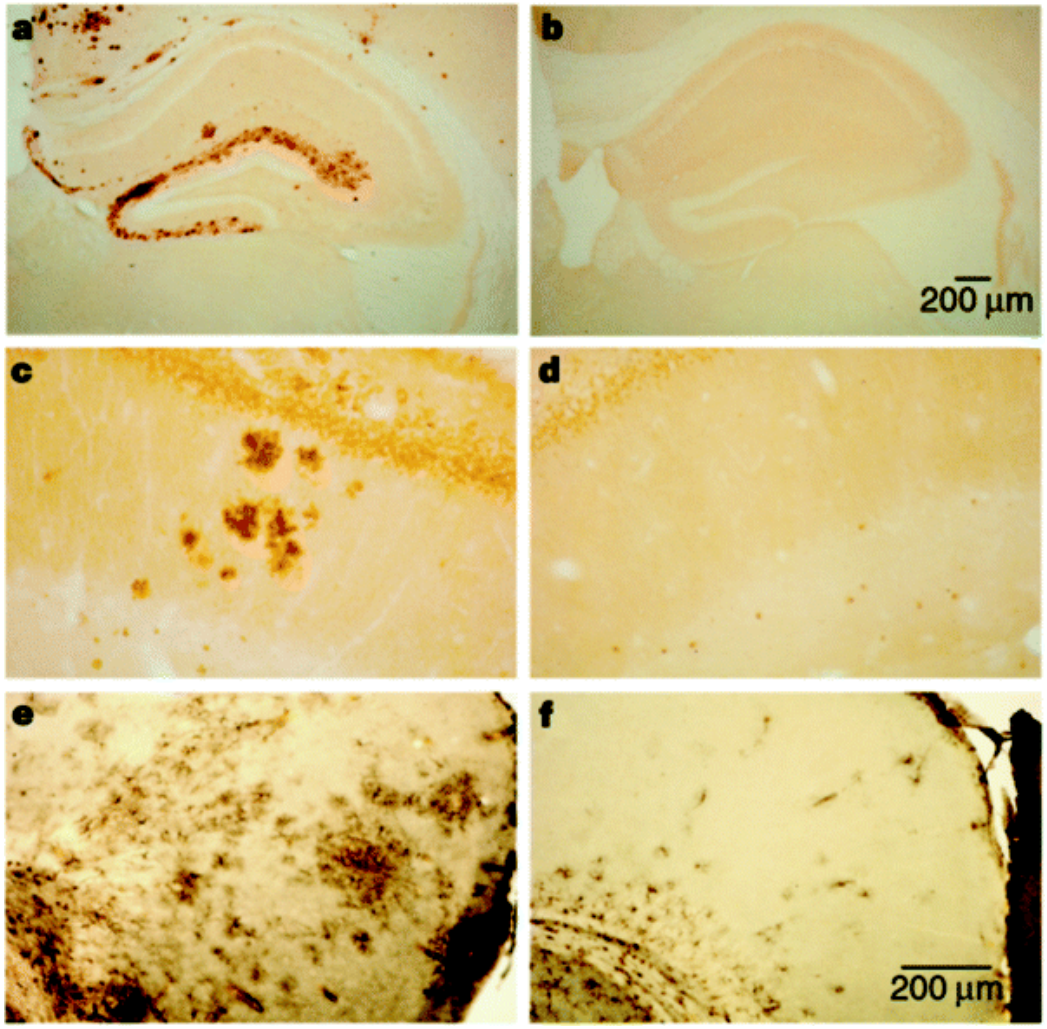




3- Enhancing Aβ degradation (IDE, NEP, CEC)

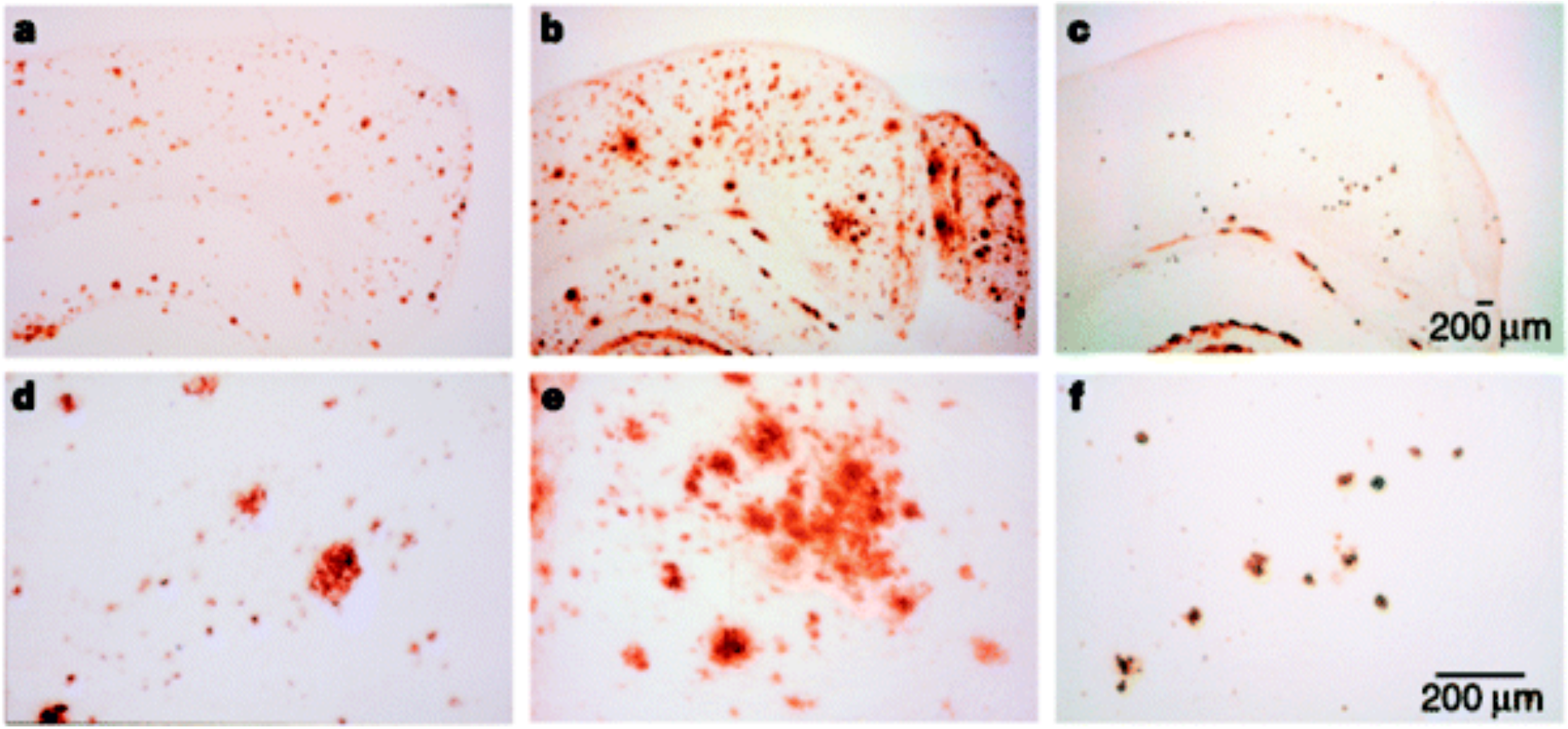
4- Inhibiting Aβ Aggregation *(Neurochem)*

Immunization of PDAPP Mice with $A\beta_{42}$ Prior to Plaque Pathology



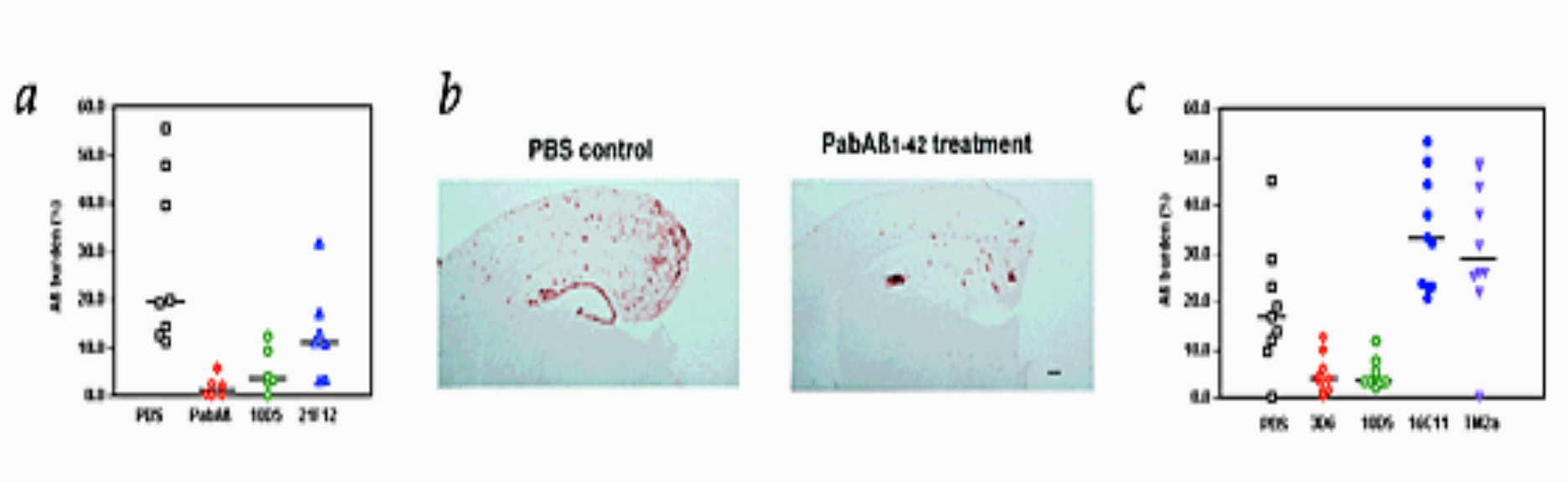
Schenk D. *et al* (1999). *Nature* **400**: 173 - 177

Immunization of PDAPP Mice with $A\beta_{42}$ After Plaque Fromation



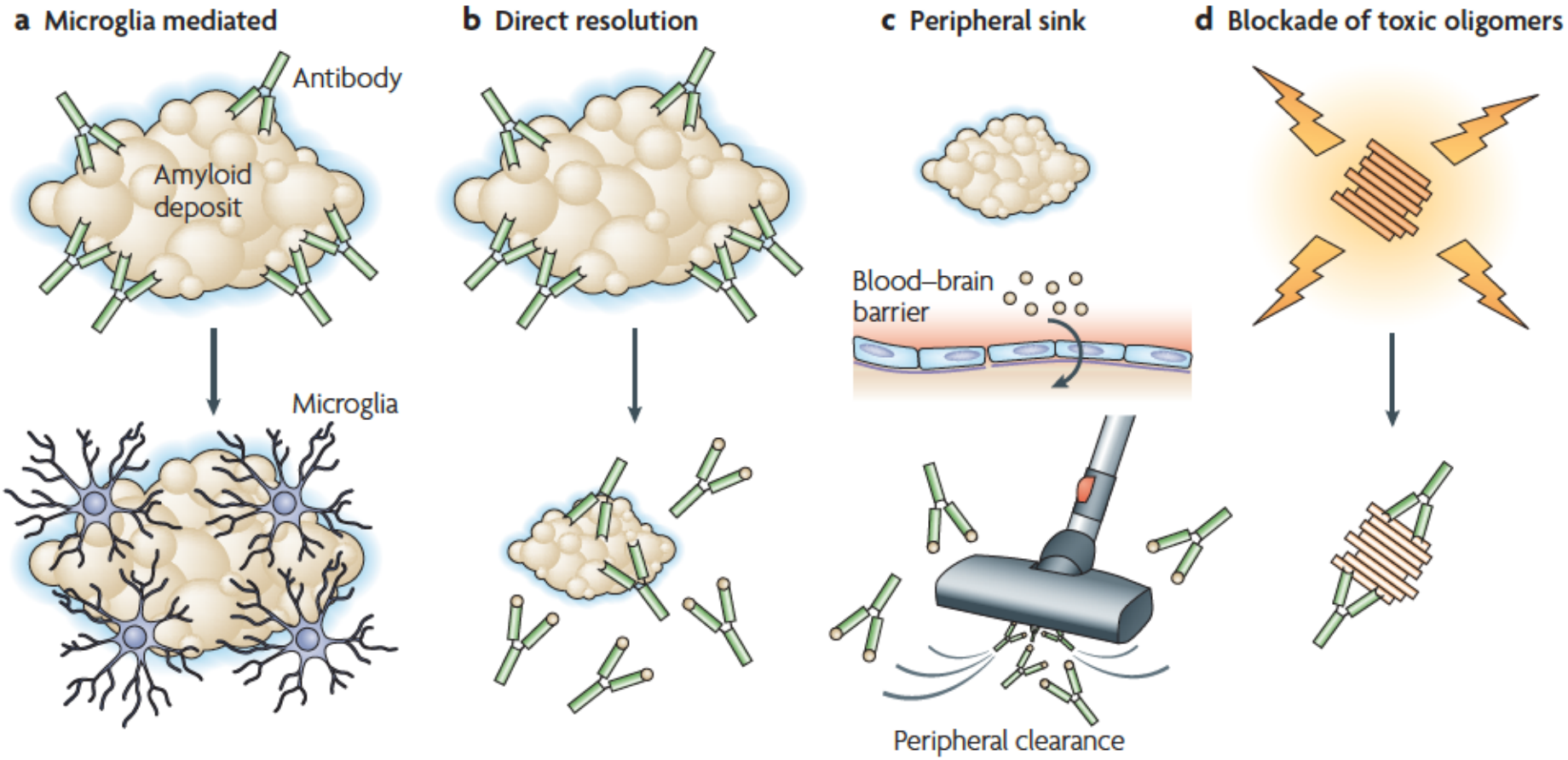
Schenk D. *et al* (1999). *Nature* **400**: 173 - 177

Passive Immunization

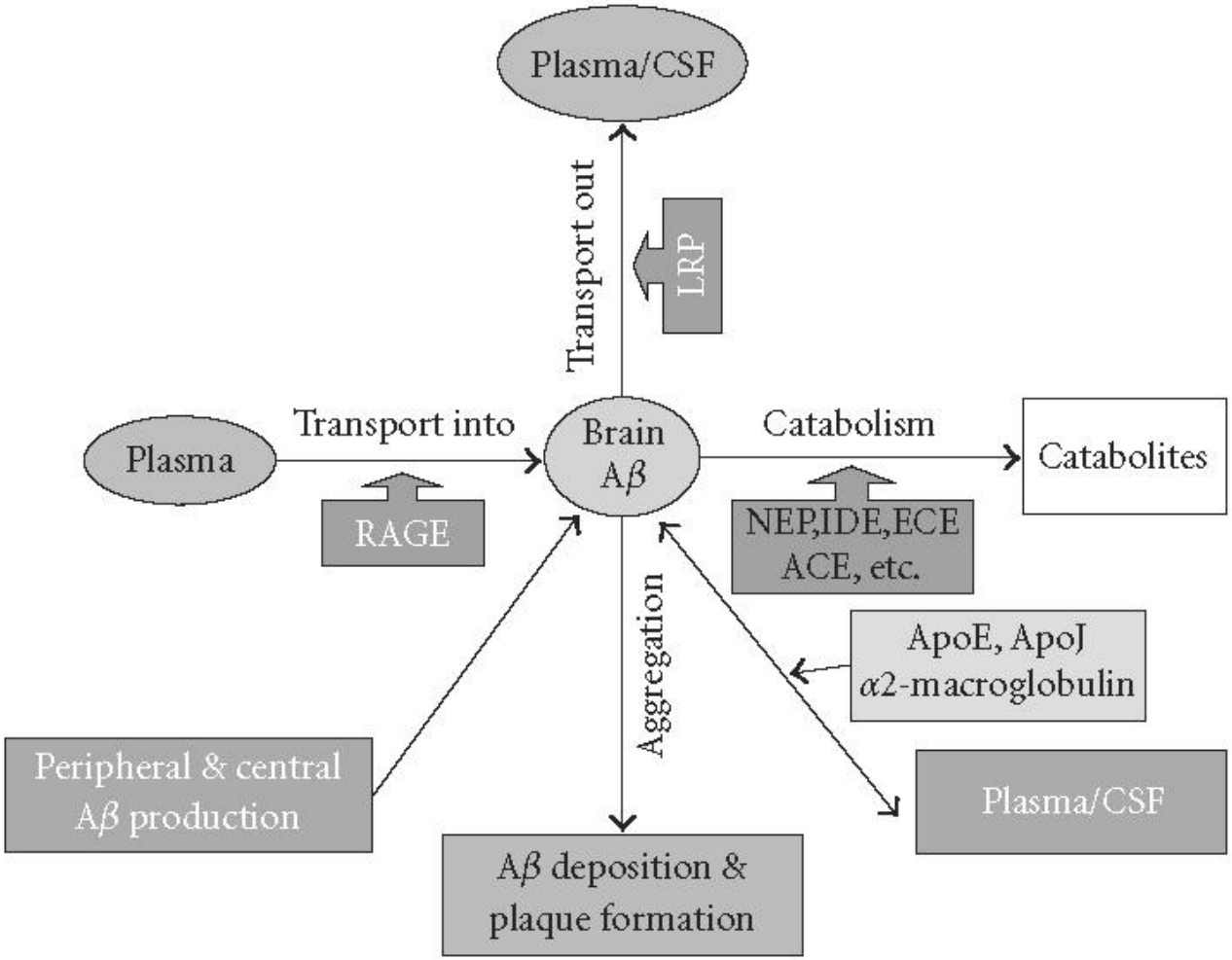


Bard F. *et al* (2000). *Nature Med.* 6 (8): 916 - 919

Antibody-mediated amyloid clearance:



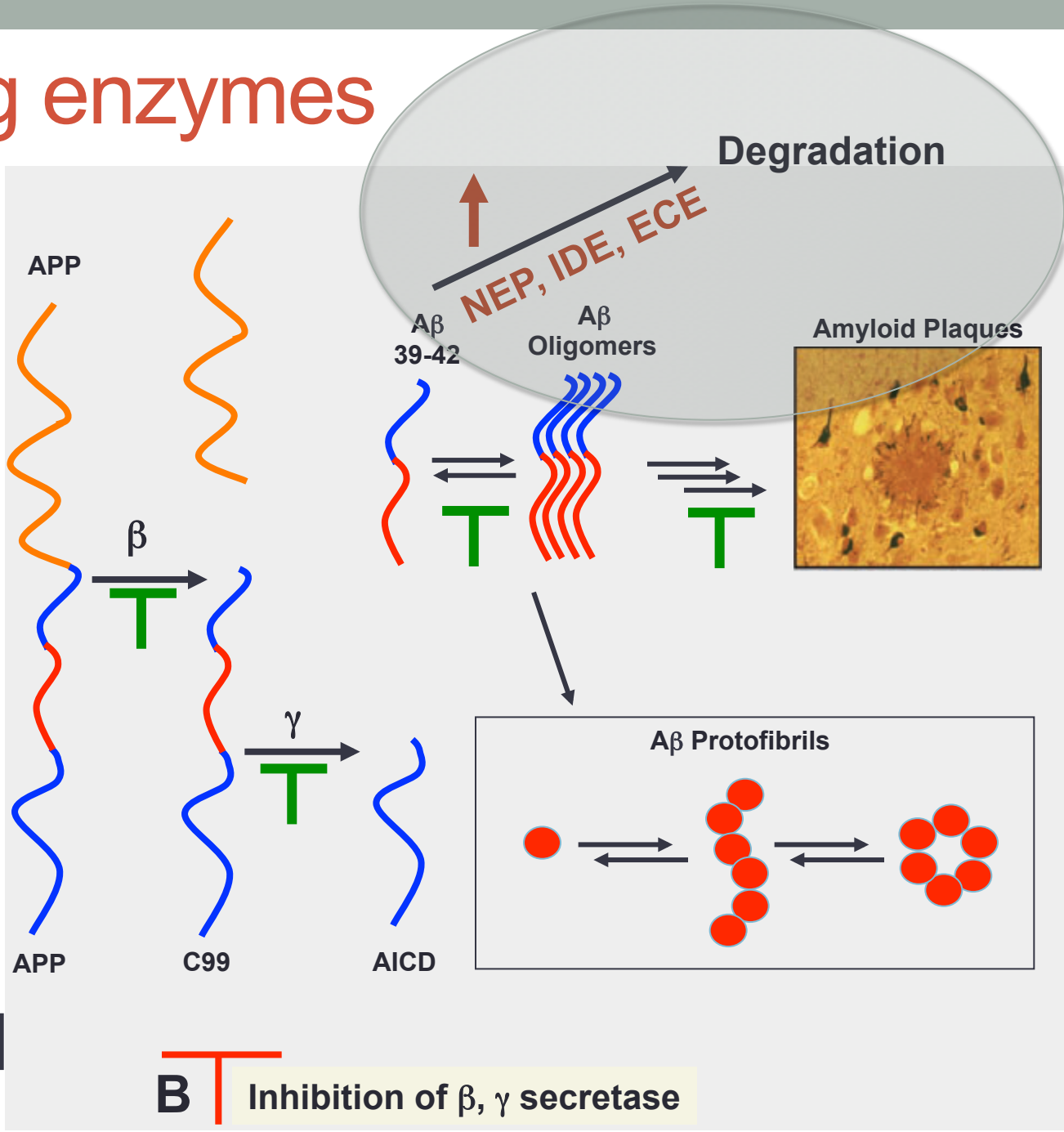
Possible brain Aβ clearance mechanisms.



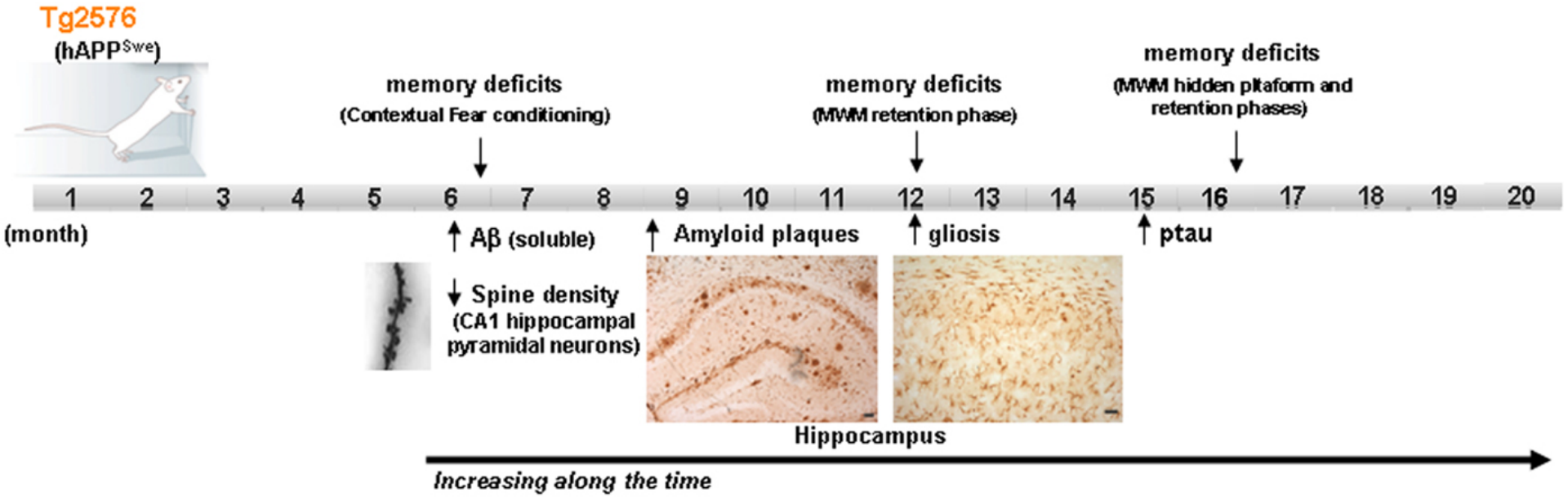
J Biomed Biotechnol. 2006; 2006: 58406.

Aβ degrading enzymes

- Neprilysin (NEP)
- Insulin Degrading Enzyme (IDE)
- Endothelin-converting enzyme.
- The levels of Neprilysin and IDE are are decreased with again and in AD brains, respectively.

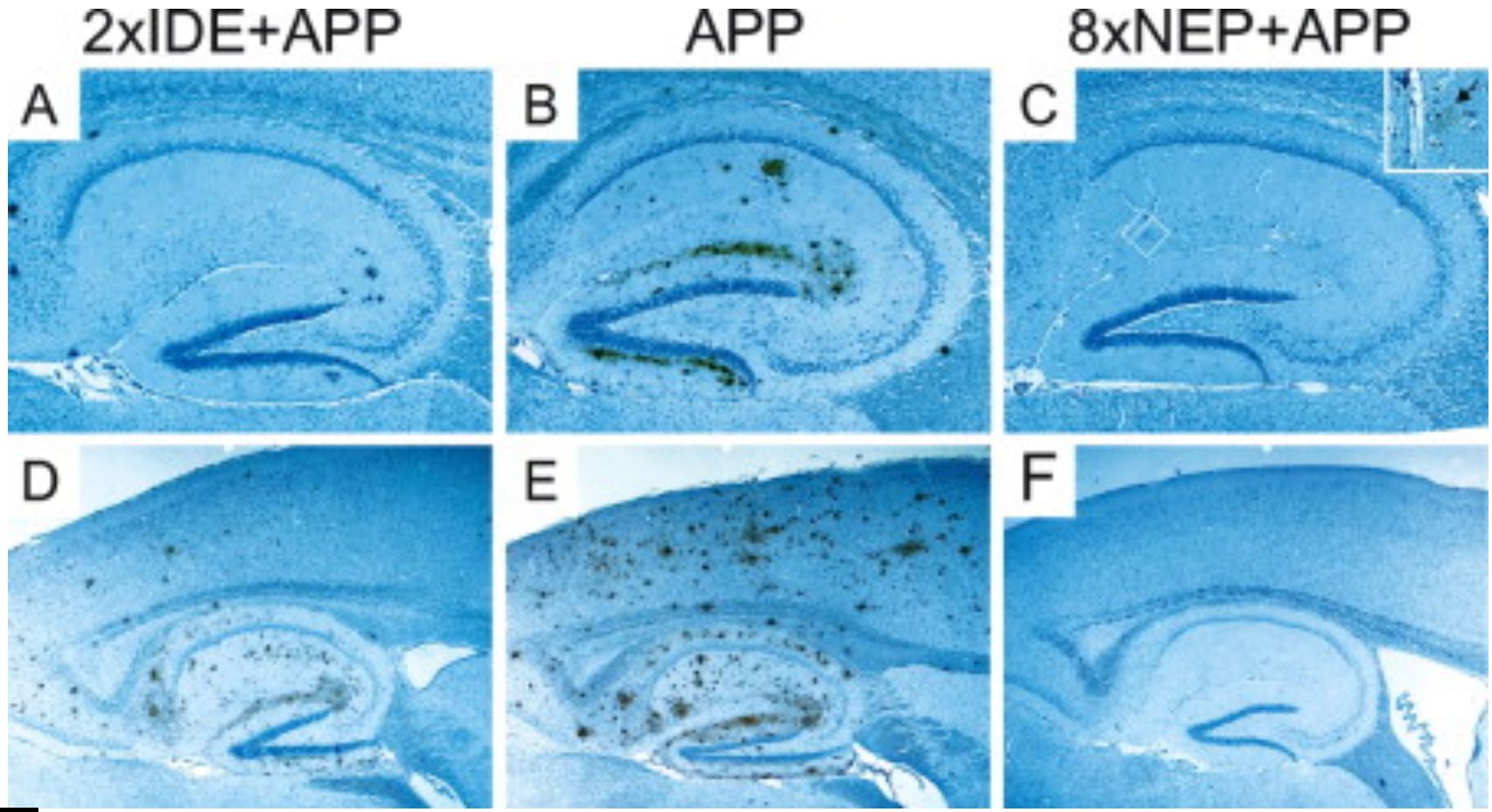


Animal Models of AD



Cuadrado-Tejedor et al., Front. Neurol., 29 September 2014

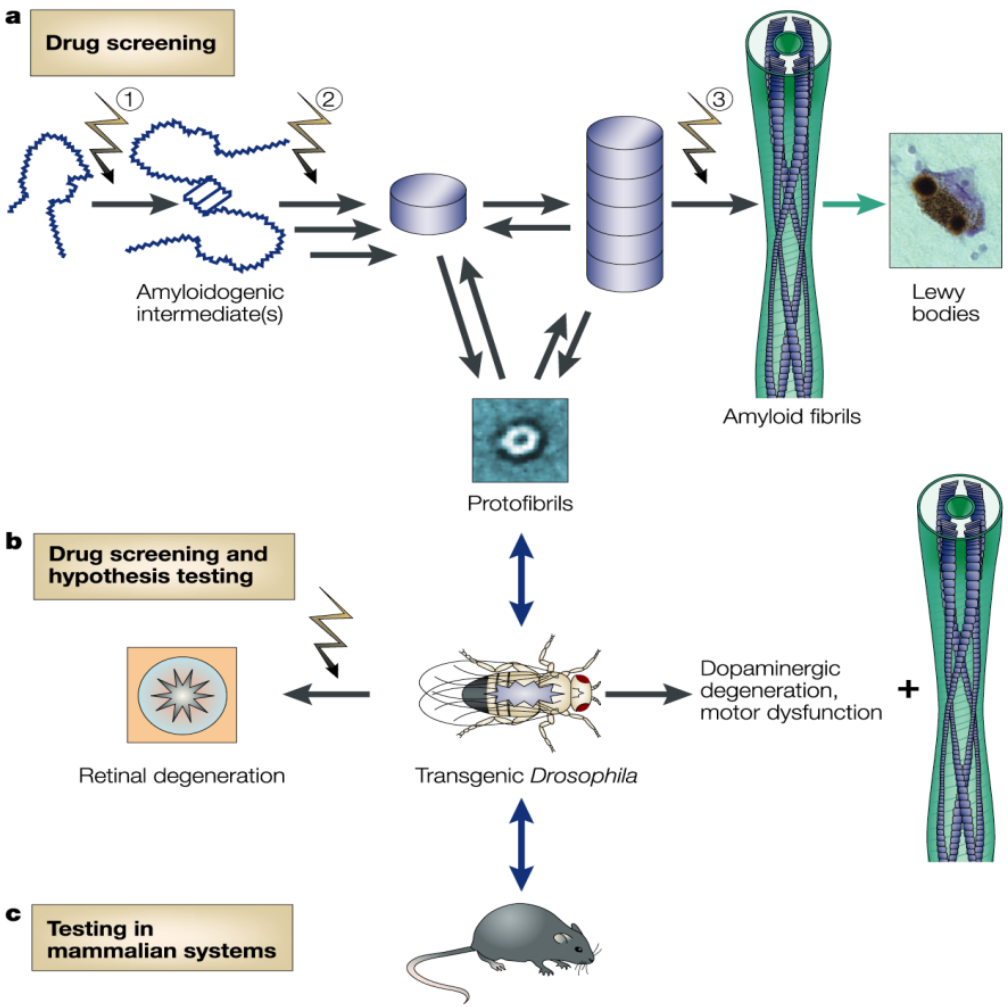
Aβ plaque burden was significantly decreased in the 2xIDE+APP and 8xNEP+APP double transgenic mice



Neuron 2003 40, 1087-1093DOI: (10.1016/S0896-6273(03)00787-6)

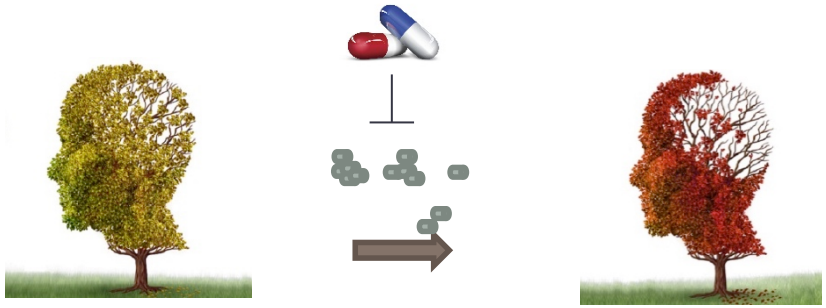
What is the mechanism?

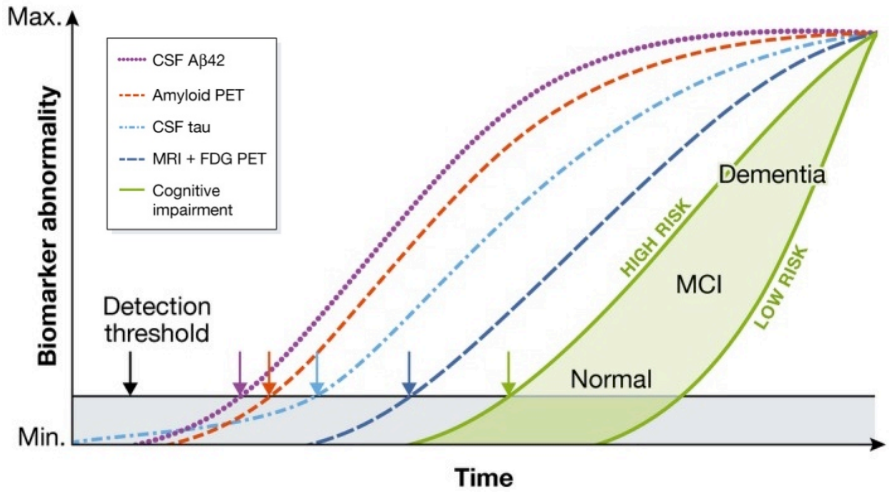
Inhibiting Aβ aggregation



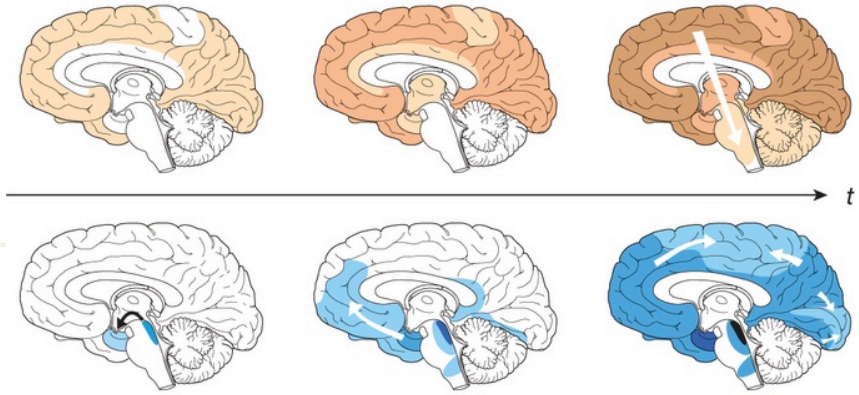
Lashuel et al, 2000

The limitations of the Amyloid hypothesis





D. J. Selkoe and J. Hardy EMBO Mol Med. 2016



Tau progression

M. Jucker and L. C. Walker, Nature, 201

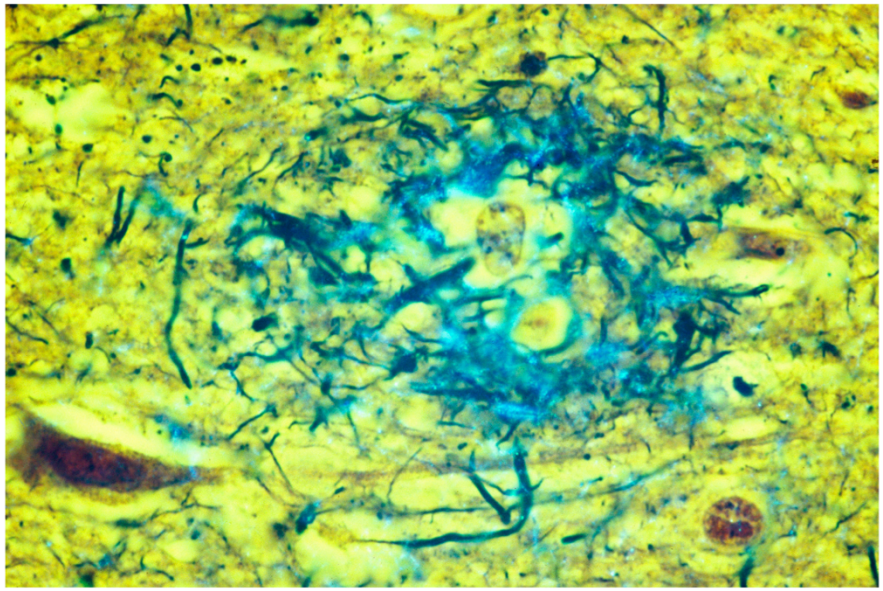
- Failure of the Aβ targeting clinical trials
- No correlation between amyloid plaque burden, progression and AD symptoms

TREATMENTS

Where Does Alzheimer's Treatment Go From Here?

December 29, 2016 · 11:00 AM ET

BRET STETKA



Diseased brain tissue from an Alzheimer's patient showing amyloid plaques (in blue) located in the gray matter of the brain.

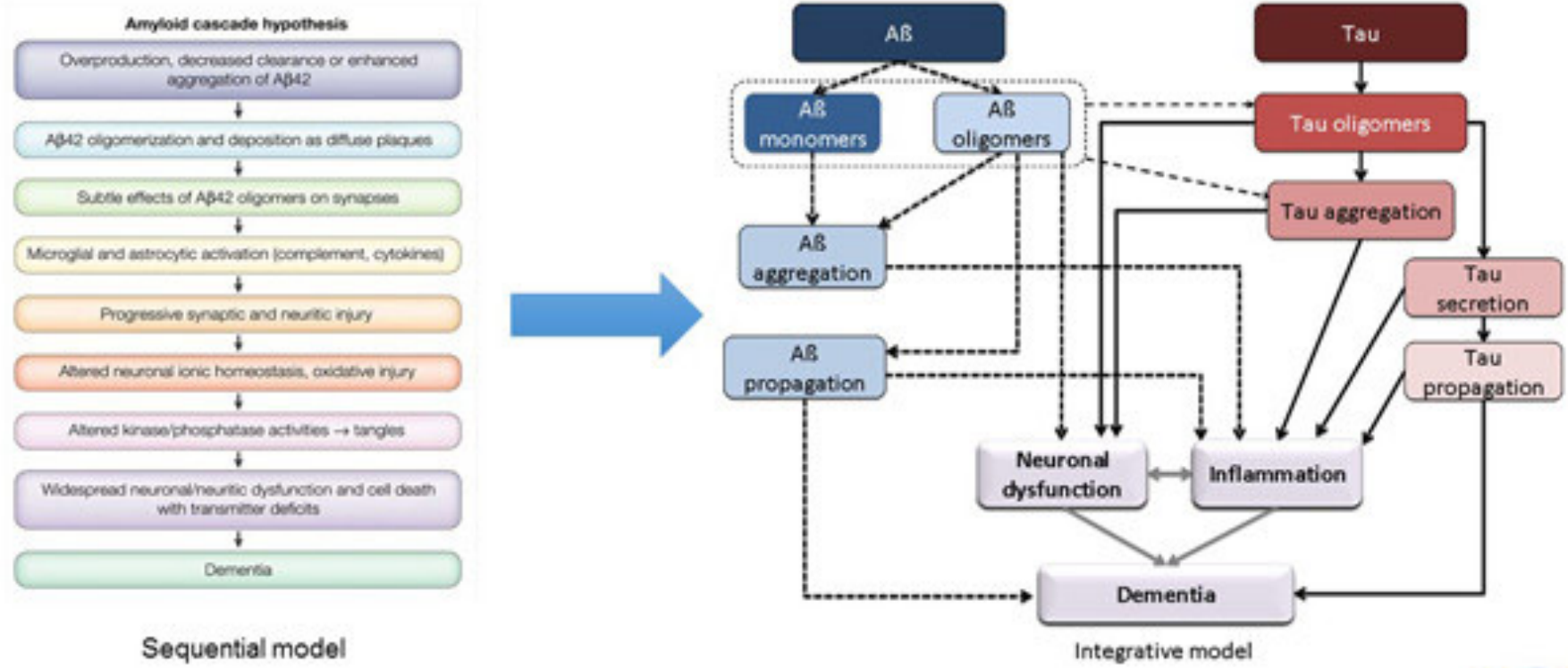
Dr Cecil H Fox/Science Source/Getty Images

Solanezumab, an antibody, works by attacking amyloid floating in cerebrospinal fluid.

"The low magnitude of effects would lend support to the idea that it might be time to move on from amyloid," says Weill Cornell Medical College neurologist Dr. Richard Isaacson,

"These trials also suggest that the best chance for a significant effect on cognition is likely to be treating asymptomatic people with amyloid deposits on imaging." Dr. James Burke

Amyloid and tau pathways need to be integrated.

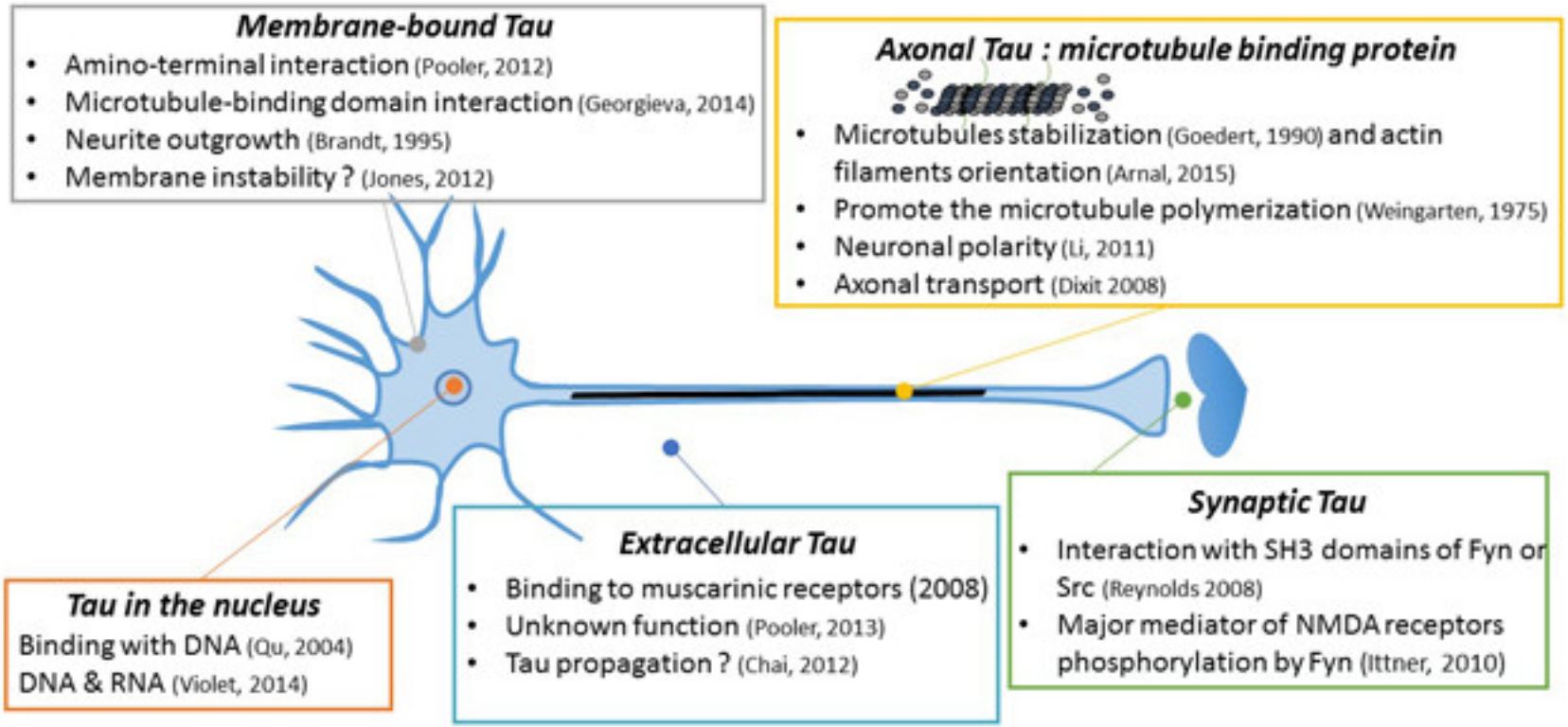


"AD comprises parallel, and often circular, pathways of proteostasis, lipid metabolism, and glial activation. Each of these pathways interact with Aβ and tau in ways that remain poorly defined"
http://www.alzforum.org

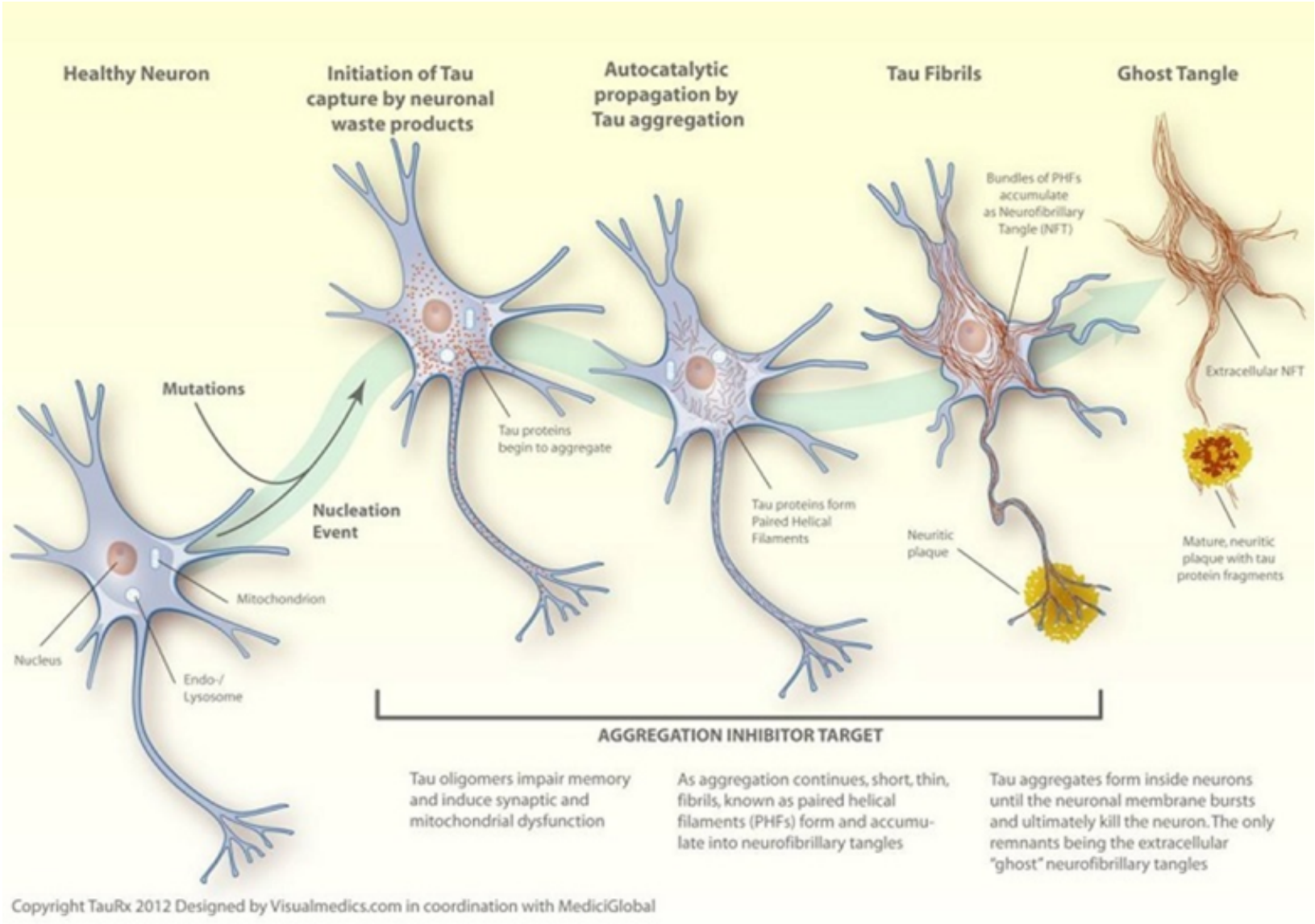
Tau pathway and neurofibrillary tangles (NFTs) hypothesis in AD

- **Targeting tau aggregates**
- **Enhancement of microtubule stabilization by tau stabilizers**
- **Prevention of tau aggregation by tau aggregation inhibitors**
- **Enhancement of phosphorylated-tau clearance by active immunotherapy**

"tau's complex biology offers many angles for therapy development"

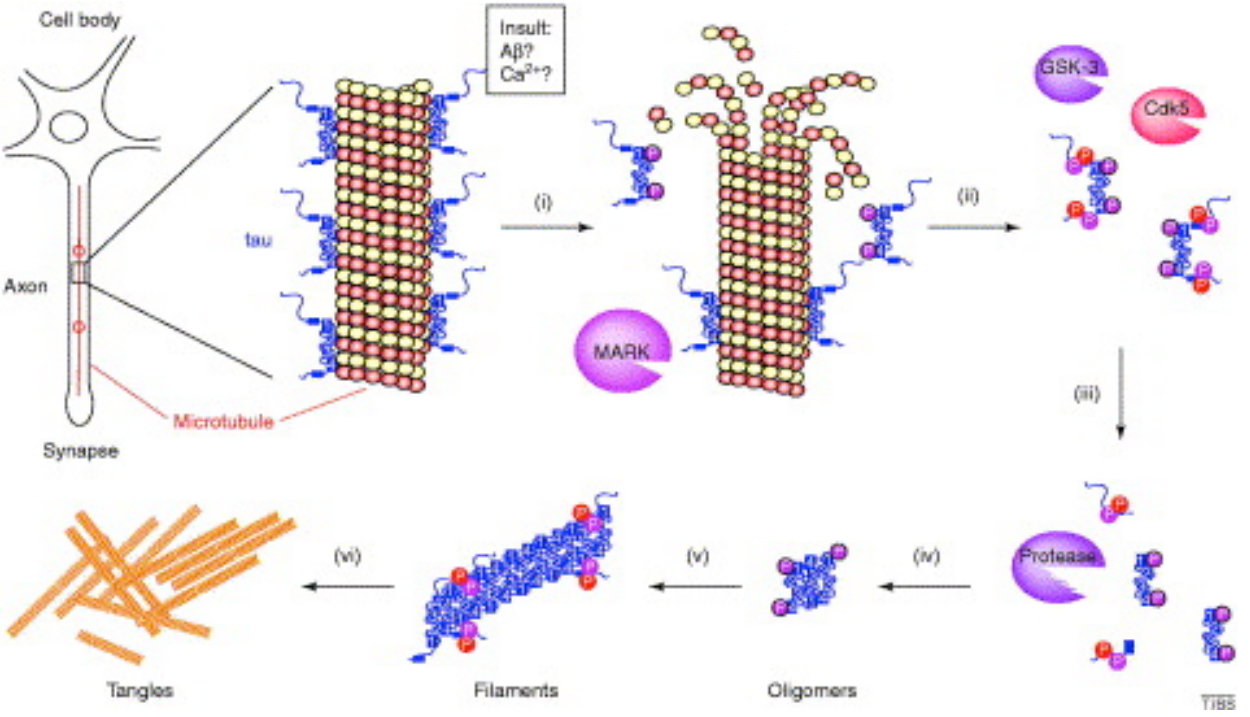


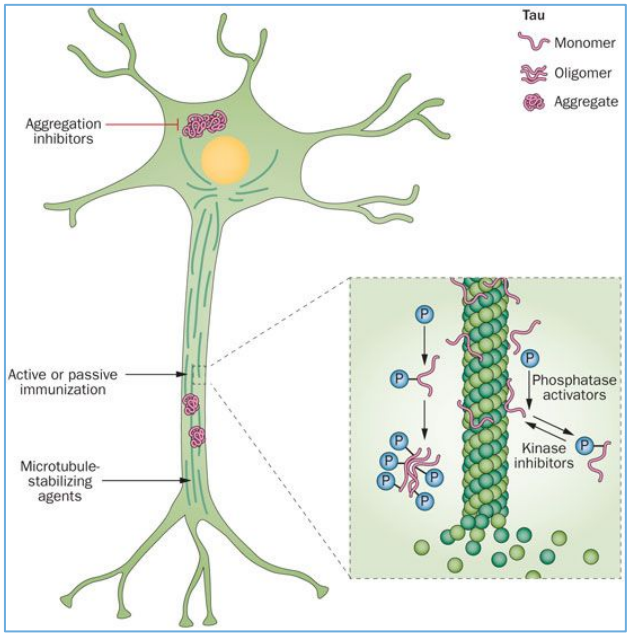
Tau Pathology



http://www.pharmafile.com

Tau –related process that represent potential therapeutic targets



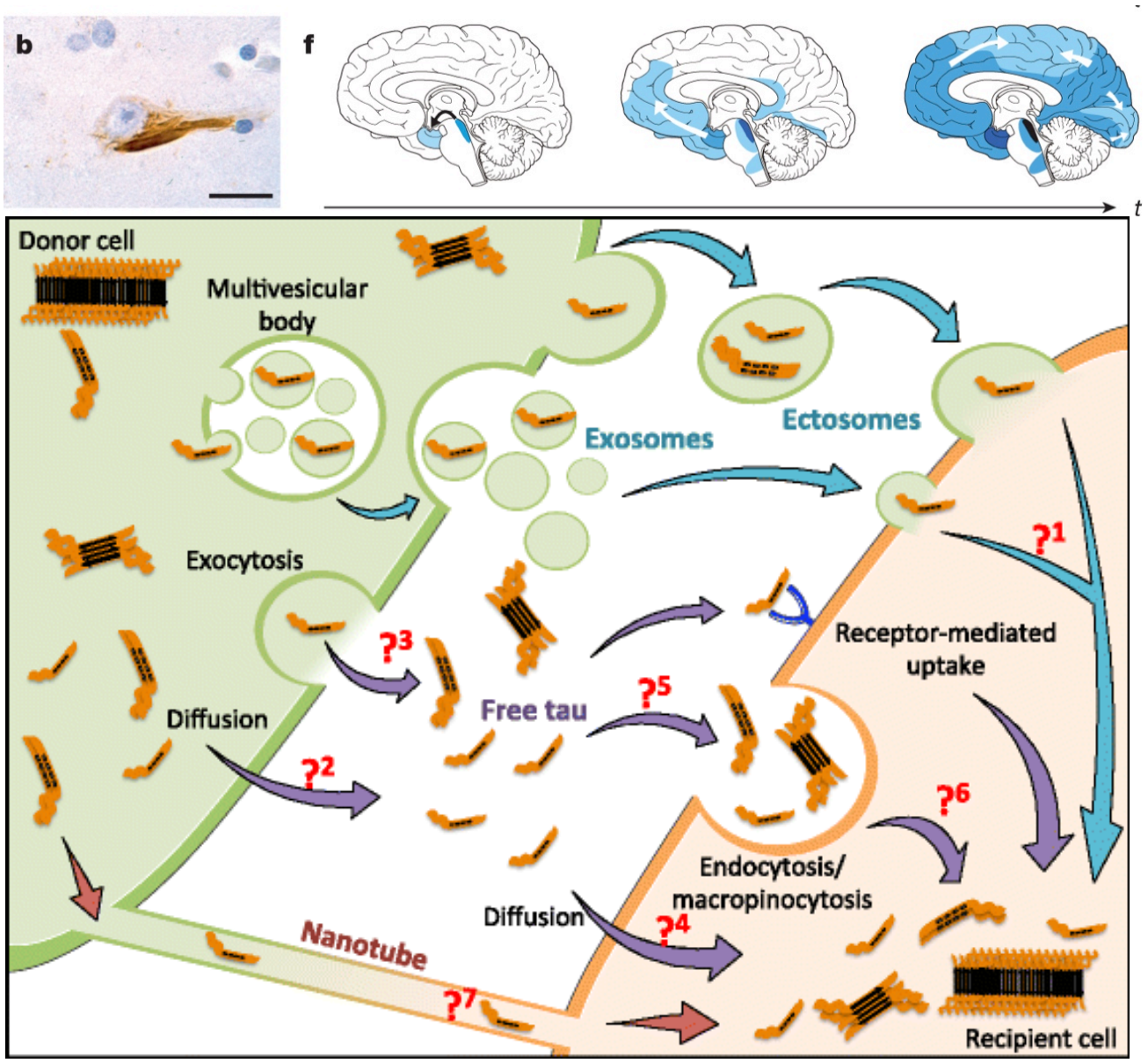


- Safe and effective Inhibitors of tau's hyperphosphorylation have not been found.

Drewes G et al., Trends in Biochemical Sciences 2004

Giacobini E et al., Nature Reviews Neurology, **9**, 677–686 (2013)

Tau – propagation



Mudher A et al., Acta Neuropath Comm. Neuro. of Disease 20175:99

M Jucker & LC Walker *Nature* **501**, 45-51 (2013) doi:10.1038/nature12481

Question 2

Assuming that Alzheimer's disease is a complex disease where multiple pathways contribute to neurodegeneration, **what would be the most effective therapeutic strategy to slow the progression of the disease after the clinical symptoms are manifested?**

Question 3

All clinical studies suggest that early intervention is the best approach for treating and preventing the progression of Alzheimer's disease.

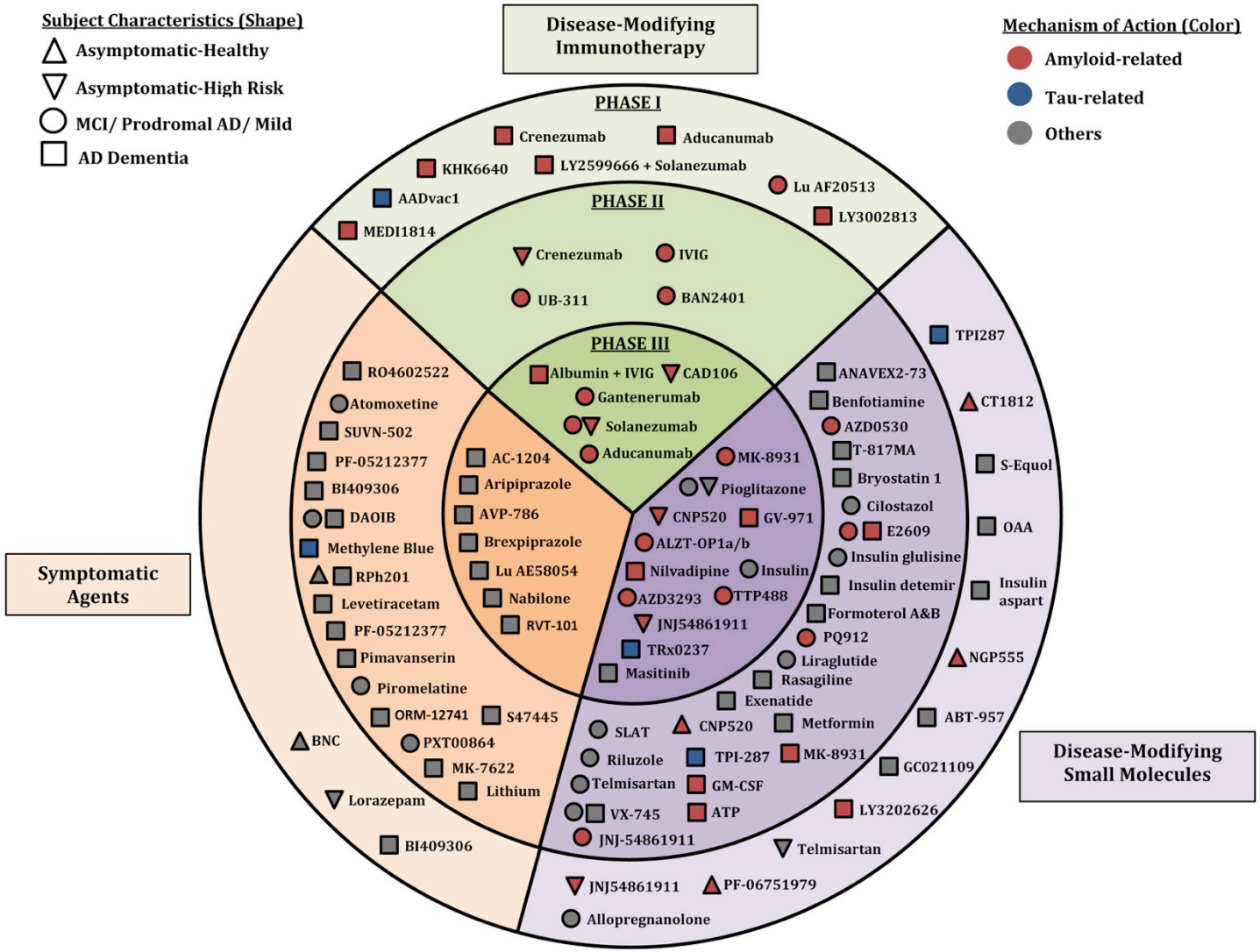
How would you go about designing a clinical trial that would enable testing the efficacy of candidate drugs at preventing or halting the disease before it starts.

Ongoing clinical trials (2016):

24 agents in 36 trials
in phase III

7 of 24 are symptomatic cognitive-enhancing compounds

17 are disease-modifying treatments (DMTs).

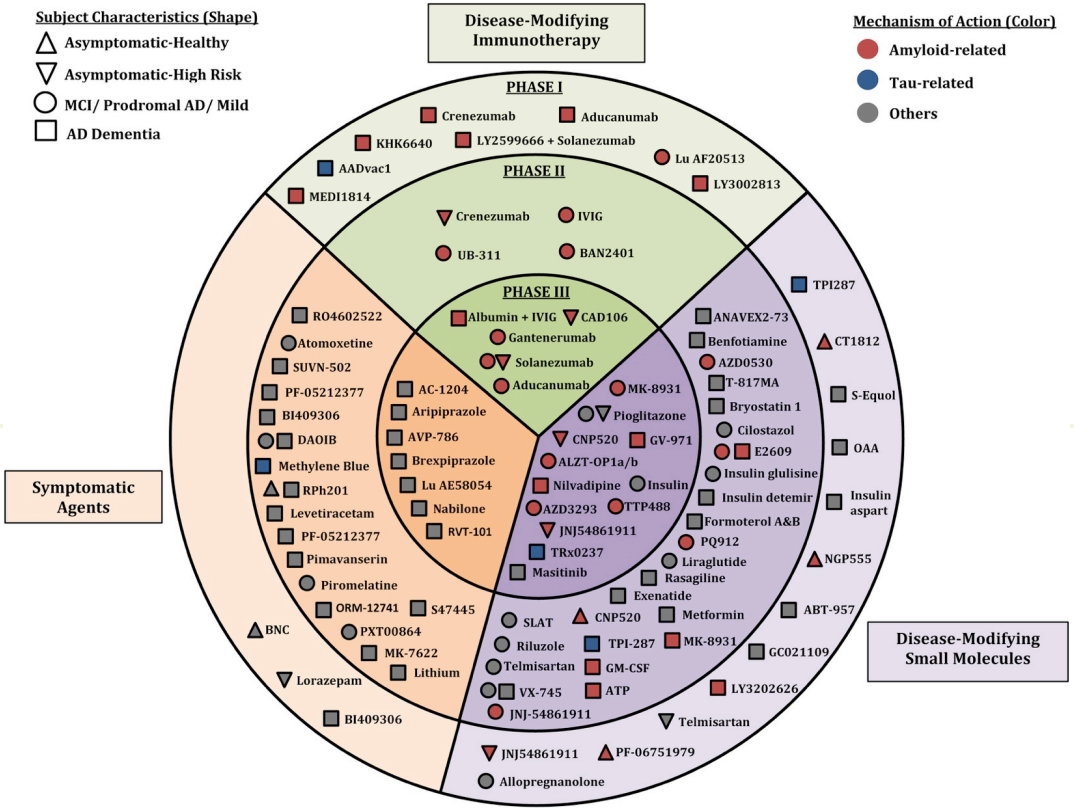


Amyloid is the most common pharmaceutical target (76%) in late development , reflecting the greater understanding of the pathophysiology of this peptide

Alzheimer's & Dementia: Translational Research & Clinical Interventions 2 (2016) 222-232

Question 4

Propose several possible explanations for the large number of drug failures in clinical trials of drugs targeting the amyloid pathway.



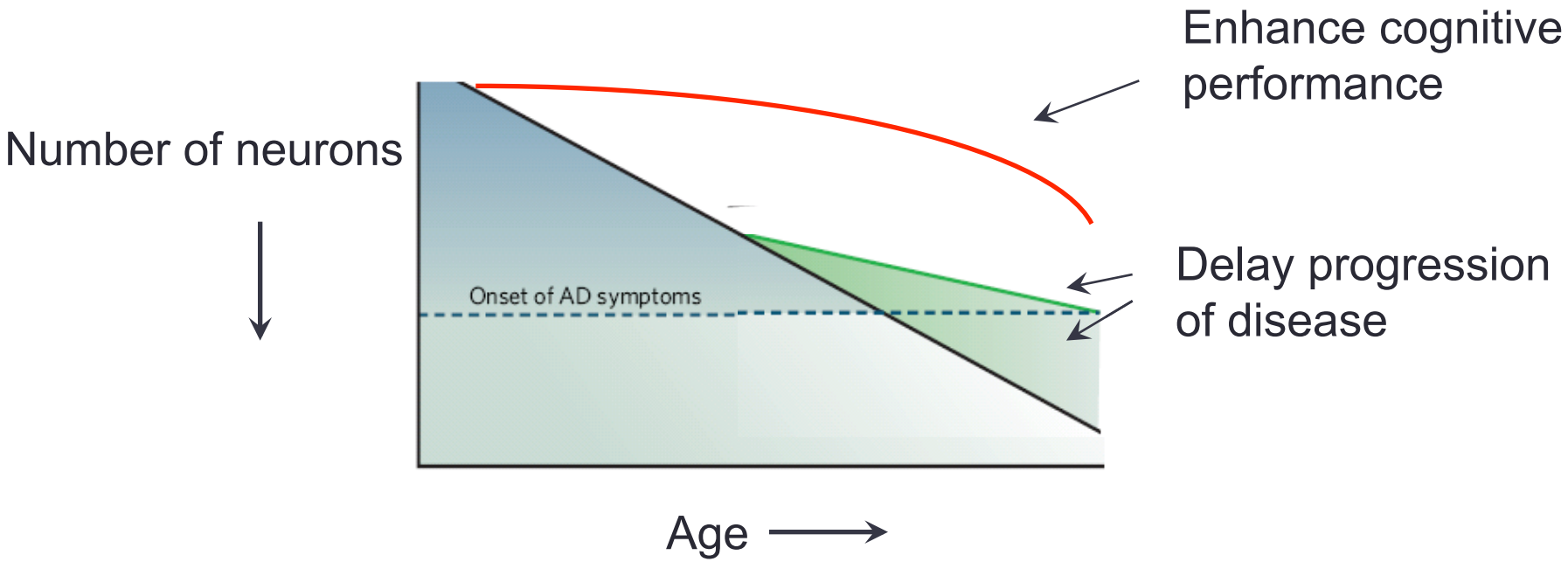
Question 4

From: Alzheimer disease therapy—moving from amyloid-β to tau

Drug	Outcome of development	Postulated cause of failure
	γ-secretase inhibitors	
Tarenflurbil	Abandoned after failed phase III trial[10]	Therapeutic concentration of drug at target not assured because of low potency and low BBB penetration
Semagacestat (LY450139)	Abandoned after two failed phase III trials[12]	Worsening of cognition, low selectivity, low BBB penetration
Avagacestat	Abandoned after phase II study[13]	Agent had low BBB penetration and was associated with worsening of cognition and risk of melanoma
	β-secretase inhibitors	
LY2886721 BACE-1 inhibitor	Abandoned after failed phase II/III trial[15]	Liver toxicity
MK-8931	Currently in ongoing phase III trial[16]	NA
	Immunization	
IVIg (gammagard)	Abandoned after failed phase II trial[17]	Treatment groups comprised too few individuals and duration of treatment was too short
AN1792	Abandoned because of meningoencephalitis in 6% of patients in a phase II trial[19]	T-lymphocyte response was too strong, antibody response was limited (observed in 20% of treated patients), and duration of treatment might have been too short
Bapineuzumab	Abandoned after failed phase III trial[24]	Low antibody response
Solanezumab	Failed to reach end points in two phase III trials[27]	Patients included in trial were too advanced to benefit
	Anti-aggregation agents	
Tramiprosate	Abandoned after failed phase III trial[31]	Drug dose might have been too low
PBT2	Results of phase IIa trials published[32]	Only two measures of executive function on the NTB improved
Scyllo-inositol	Abandoned after failed phase II trial[33]	Unexpected death and infections after treatment

Abbreviations: BACE-1, β-secretase 1; BBB, blood–brain barrier; NBT, neuropsychological test battery.

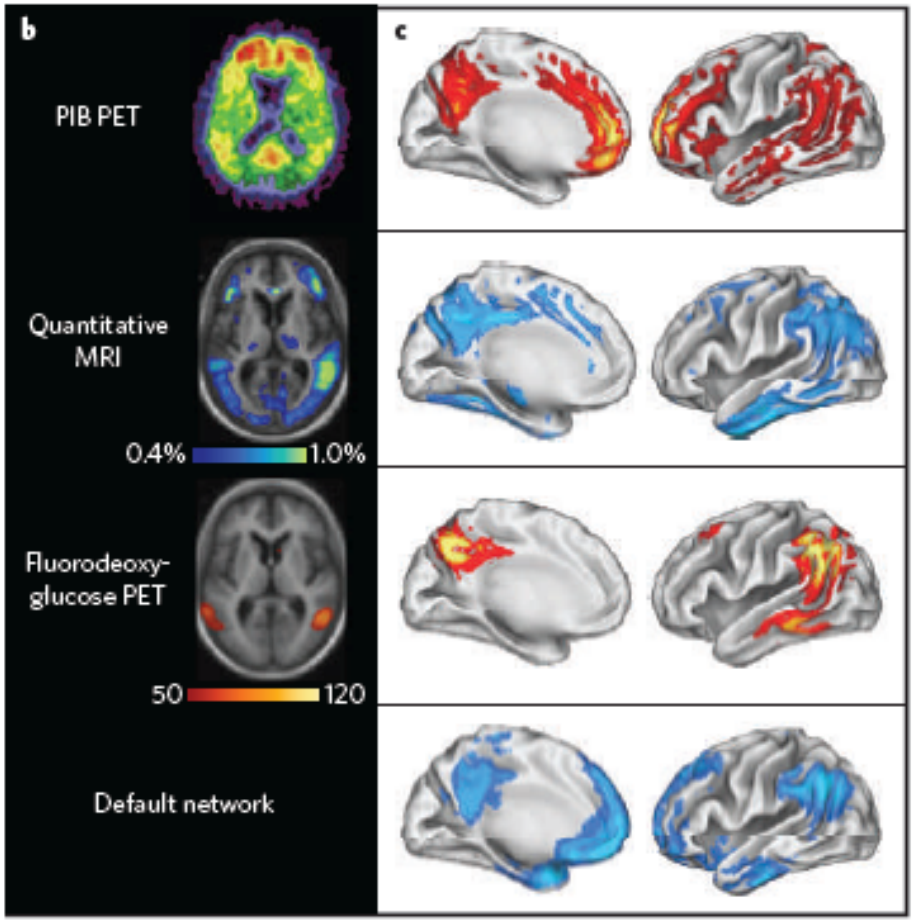
Better Peripheral Biomarkers and tools to monitor the progression of the pathogenic process are key to presymptomatic diagnosis and treatment of neurodegenerative disease



Lansbury & Lashuel, 2006, Nature

AD Diagnostics

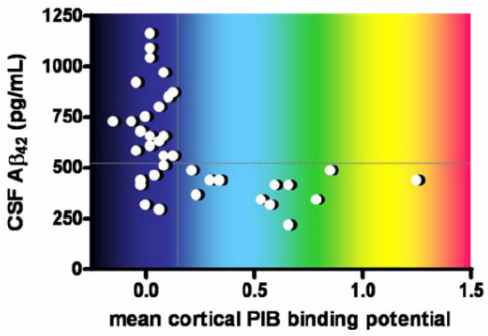
- Diagnostic tools:
  - Mental examination
  - PIB PET
  - Quantitative MRI
  - Fluorodeoxyglucose PET
  - More experimental approaches

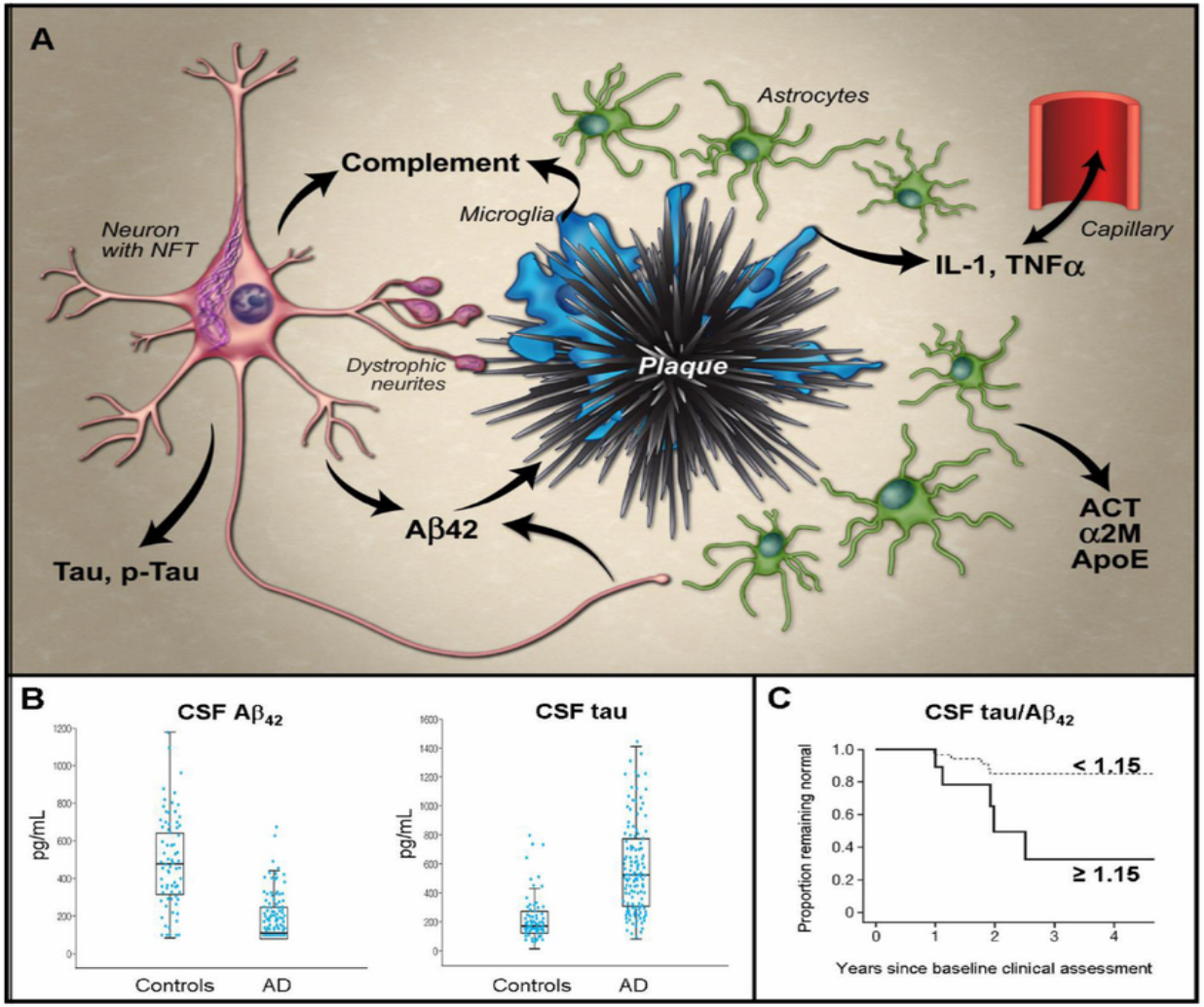


Perrin RJ et al., Nature 2009

Fluid biomarkers

CSF Aβ42 is significantly reduced in AD subjects.
Why??

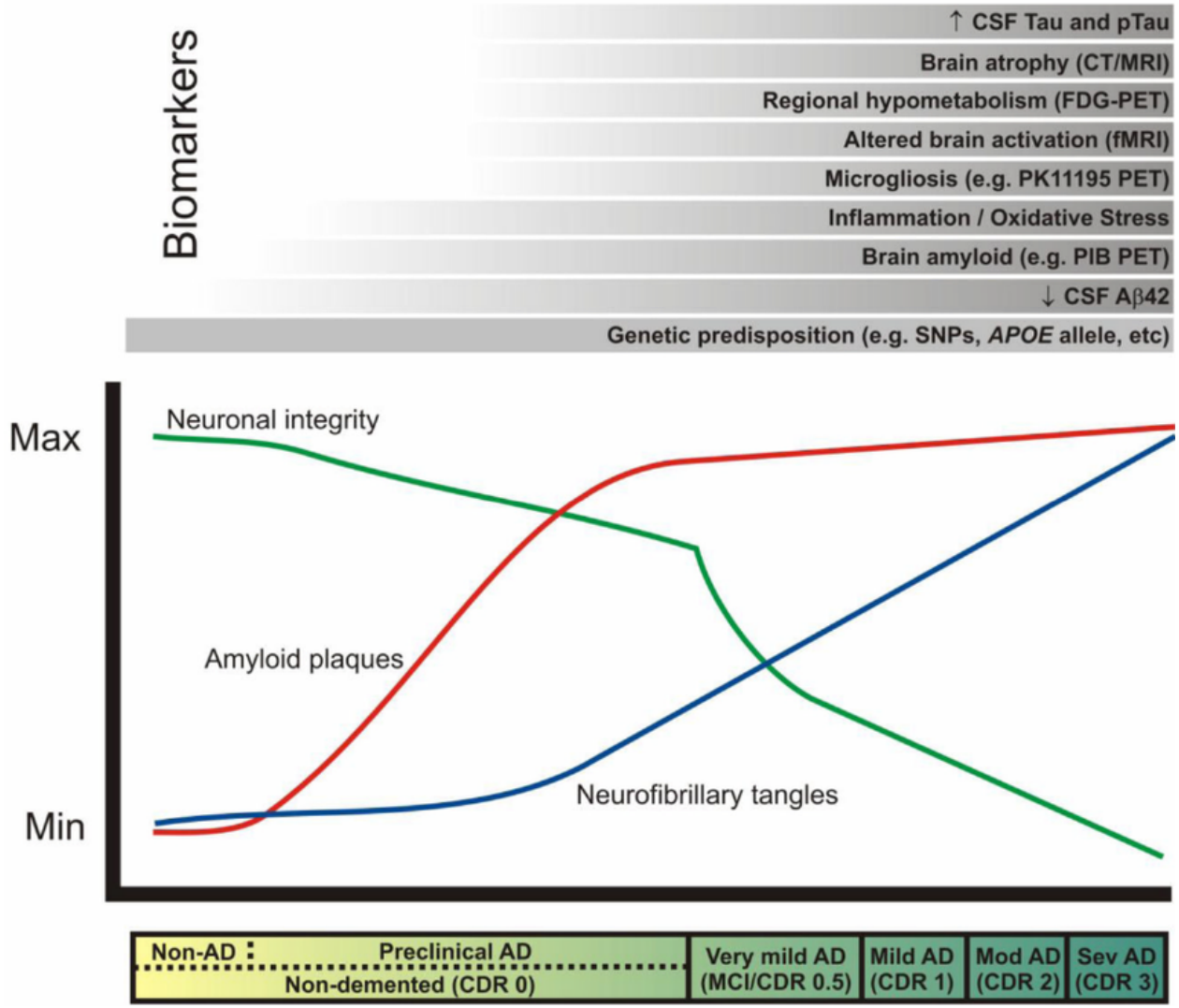




Perrin RJ et al., Nature 2009

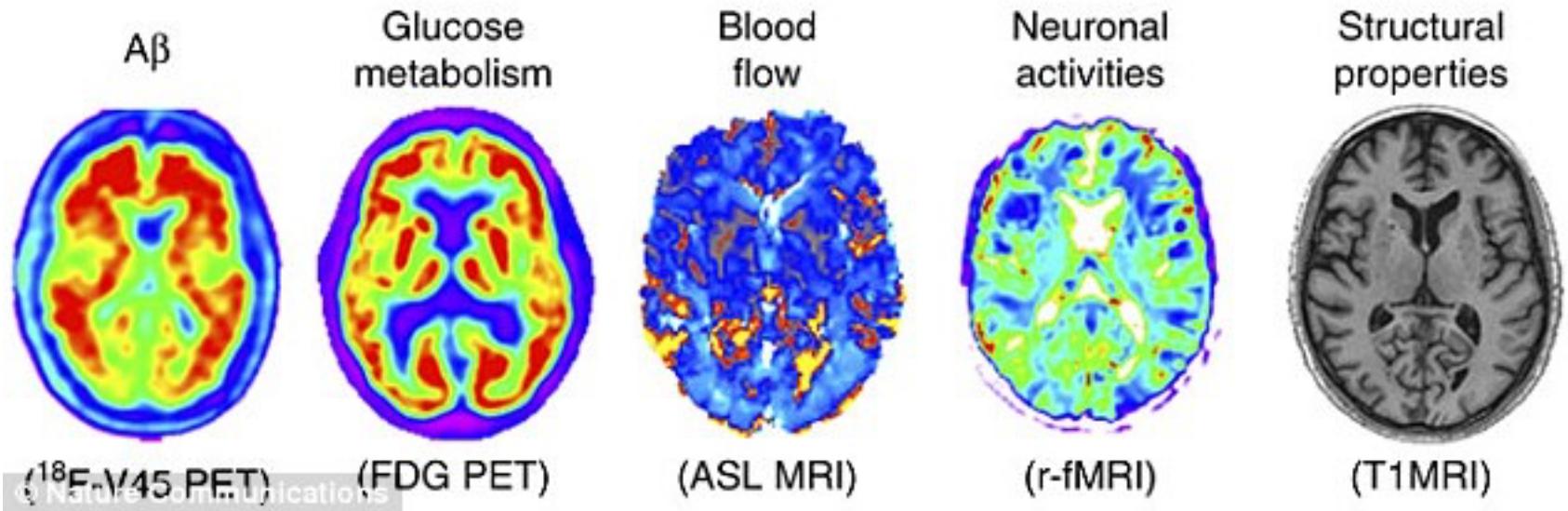
Pathophysiological hallmarks

Biomarkers and AD: proposed changes in biomarkers in relation to time course of pathological and clinical stages



Perrin RJ et al., Nature 2009

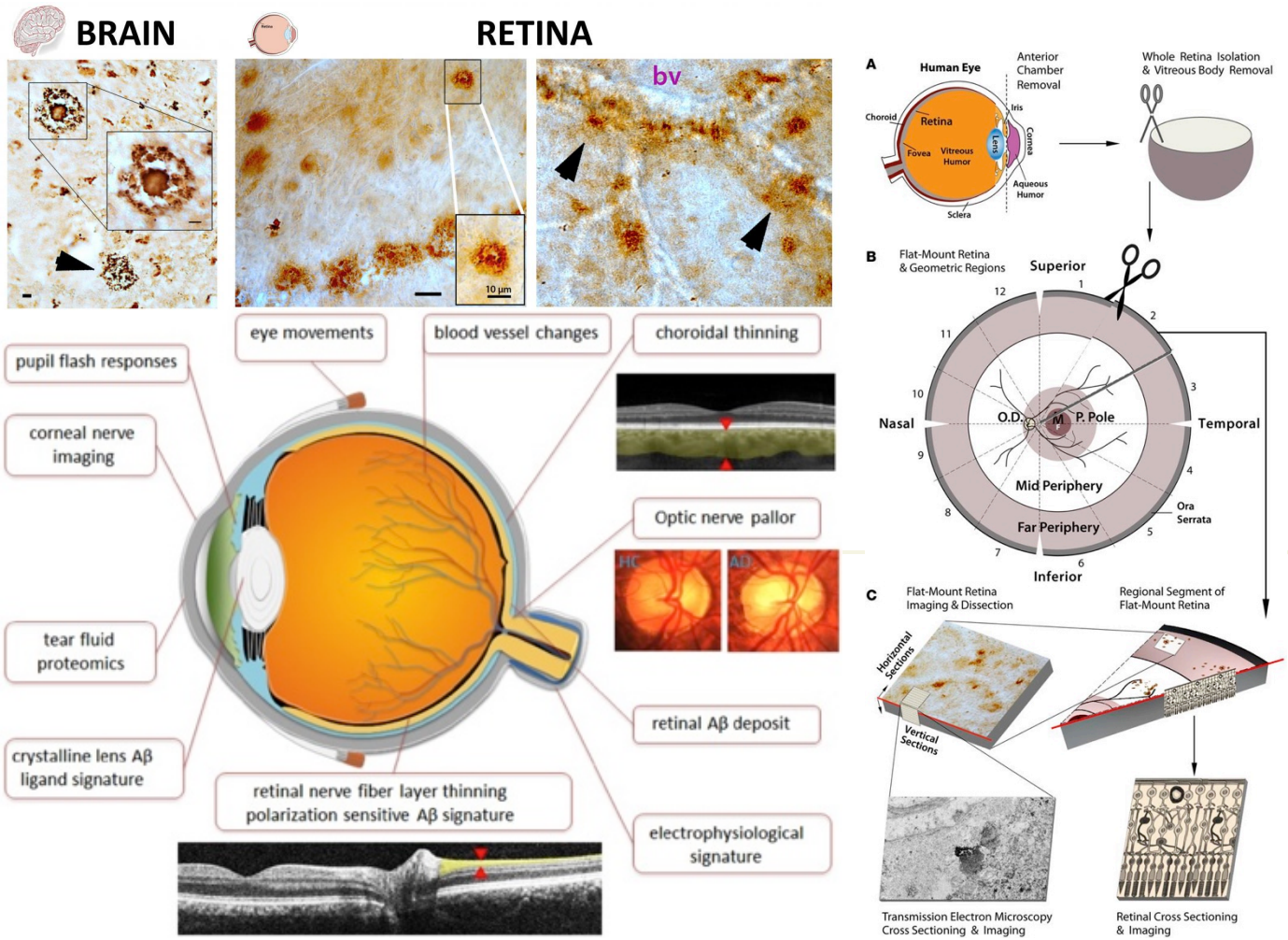
Multimodal Imaging of Alzheimer Pathophysiology



- Amyloid concentration
- glucose metabolism
- cerebral blood flow
- functional activity
- brain atrophy

http://www.dailymail.co.uk/health/article-3687192/Decrease-blood-flow-brain-earliest-sign-Alzheimer-s-scientists-discover-thorough-study-published-disease.html

Clinical study shows that retinal imaging may detect signs of Alzheimer's disease



Koronyo Y et al., JCI Insight. 2017;2(16):e93621.

Question 6

A recent study reported that a mutation in gene that code for protein X is associated with early onset form of Alzheimer's disease . Outline different experimental approaches to establish the relevance and mechanisms by which this mutations/protein X contributes to the pathogenesis of Alzheimer's disease.

Question 7

Protein aggregation: Design experiments to determine if protein aggregation is the cause or a consequence of the neurodegenerative diseases