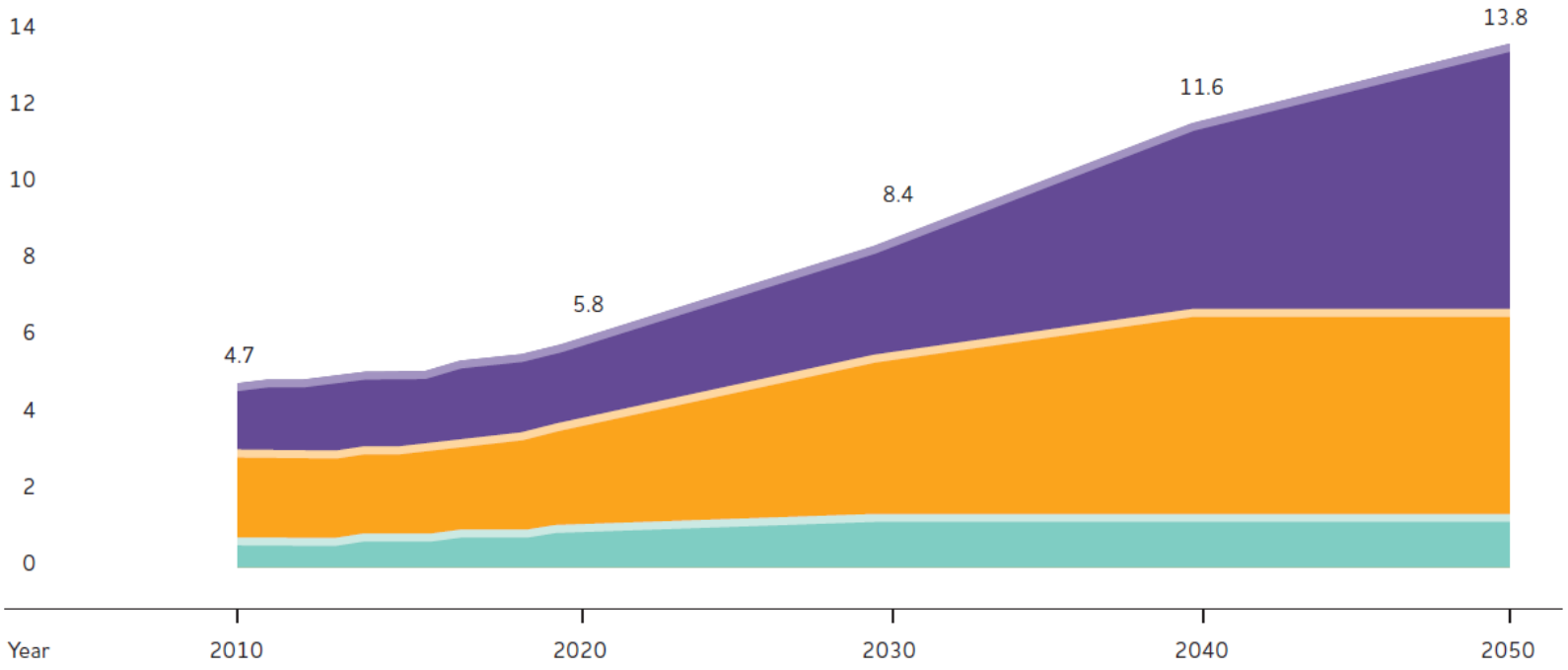
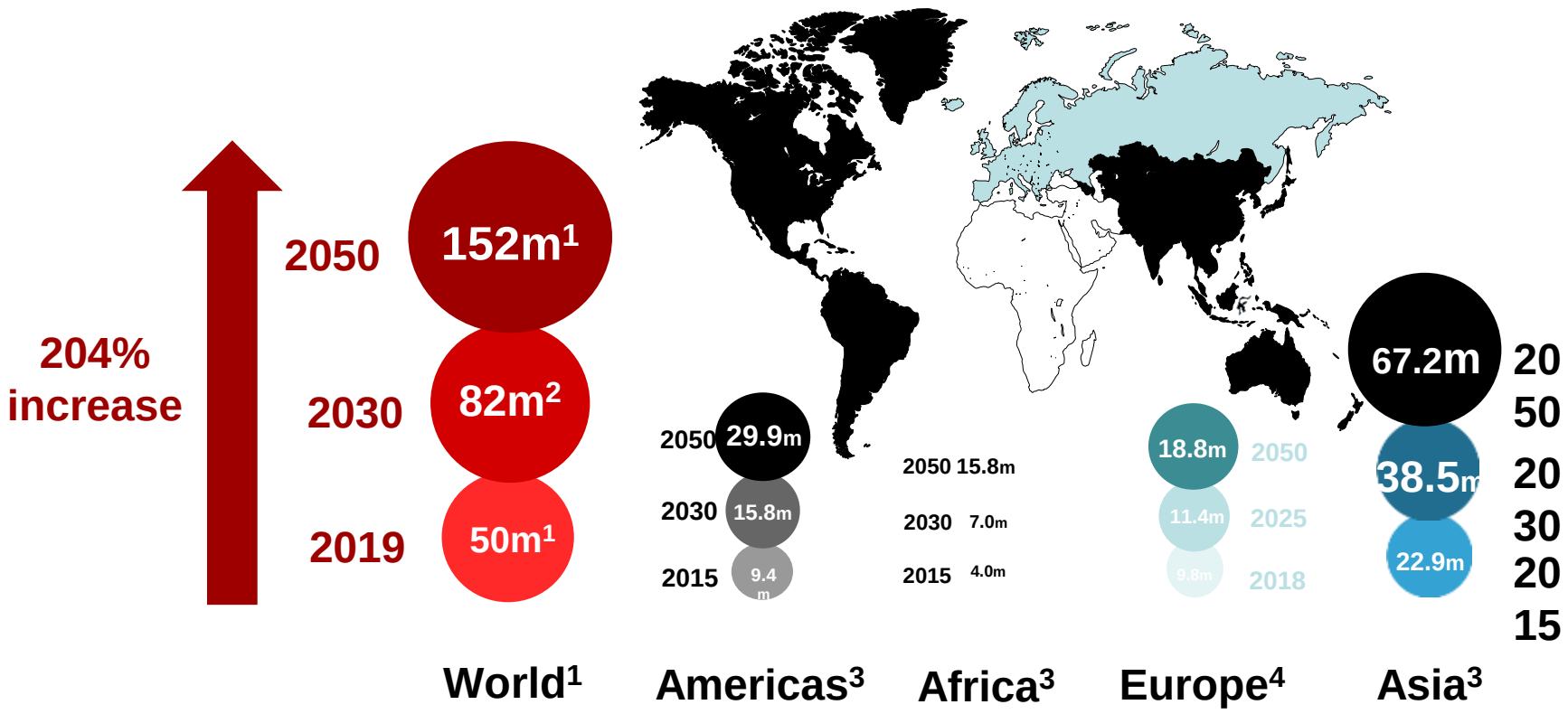
Neurodegenerative disorders:
Next years pandemic

FIGURE 4 Projected Number of People Age 65 and Older (Total and by Age Group) in the U.S. Population with Alzheimer's Disease, 2010 to 2050



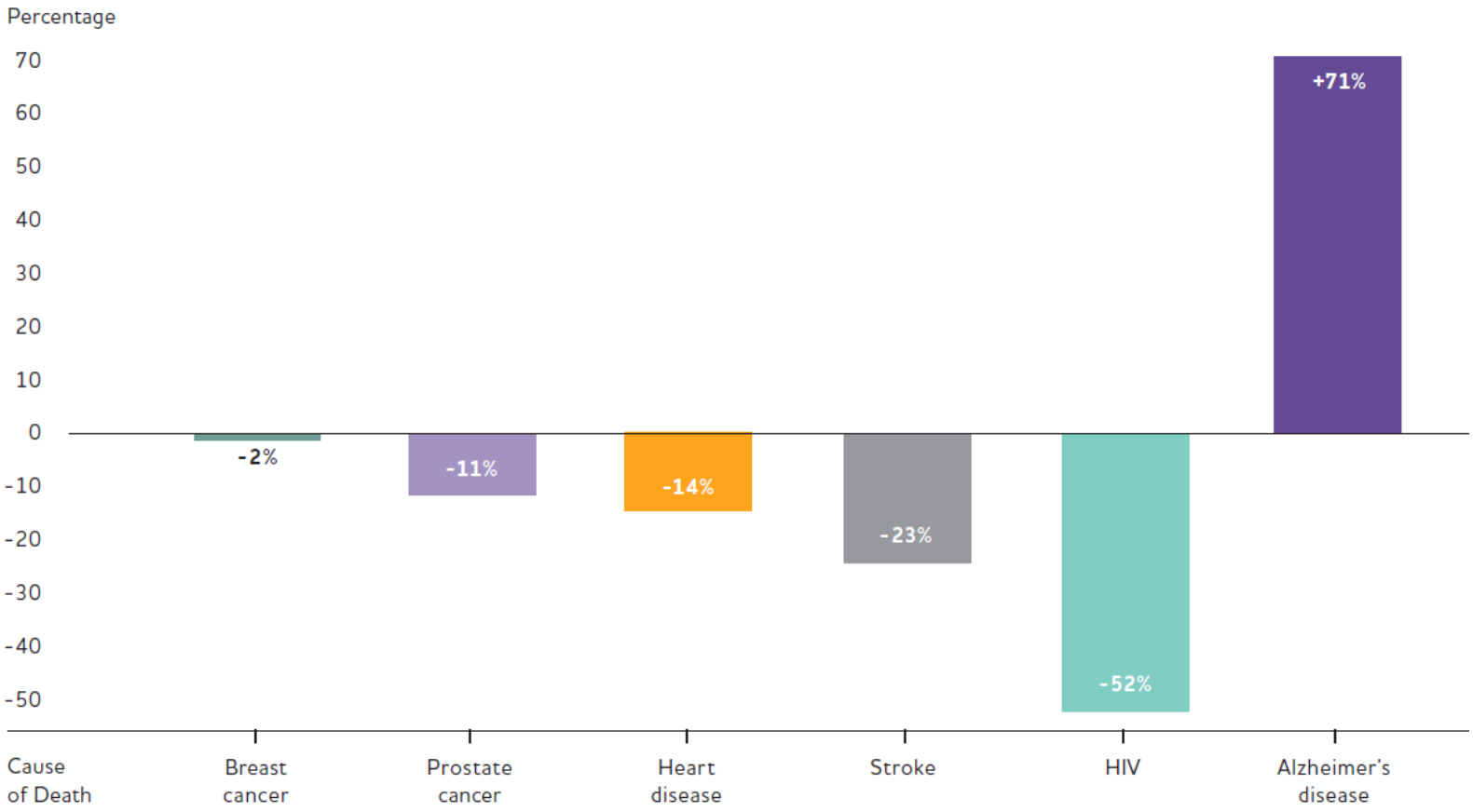
Created from data from Hebert et al.[33,A12]

Estimated prevalence of dementia is projected to double every 20 years



1. Alzheimer's Disease International: World Alzheimer Report 2019. Available from: https://www.alz.co.uk/research/WorldAlzheimerReport2019 (Accessed February 13, 2020); 2. Alzheimer's Disease International: World Alzheimer Report 2018. Available from: https://www.alz.co.uk/research/WorldAlzheimerReport2018.pdf?2 (Accessed November 12, 2018); 3. Alzheimer's Disease International: World Alzheimer Report 2015. Available from: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf (Accessed November 12, 2018); 4. Alzheimer Europe Dementia Yearbook Report 2019. Available from: https://www.alzheimer-europe.org/Publications/Dementia-in-Europe-Yearbooks (Accessed March 13, 2020)

FIGURE 5 | Percentage Changes in Selected Causes of Death (All Ages) Between 2000 and 2013



Created from data from the National Center for Health Statistics.[180]

NEURODEGENERATIVE DISORDERS

CLINICAL CHARACTERISTICS

- **slow and sneaky onset**
- **progressive course**
- **in general simmetric symptoms and signs**
- **age correlation**
- **clinical presentation reflects primitive involvement of some neuronal systems**
- **overlap between disorders**

GENETIC CHARACTERISTICS

- **Rare forms with mendelian pattern**
- **Different Mutations: puntiform - deletions- esonic or intronic expansions**
- **Variable penetrance – interacting genetic, epigenetic and env. factors**
- **Some mitochondrial transmission (matrilinear)**
- **High prevalence of sporadic forms, with genetic risk factors (polymorphisms)**

Anatomo-pathologic features

- **Apoptosis and progressive neuronal death**
- **Synaptic dysfunction**
- **Involvement of correlated neuronal systems**
- **Microglia involvement (neuroinflammation)**
- **Misfoded proteins accumulation**

PATHOLOGY PRECEDES SYMPTOMS BY YEARS

PATHOLOGY: FROM MOLECULES TO NETWORKS

Degenerative process

Onse[redacted]

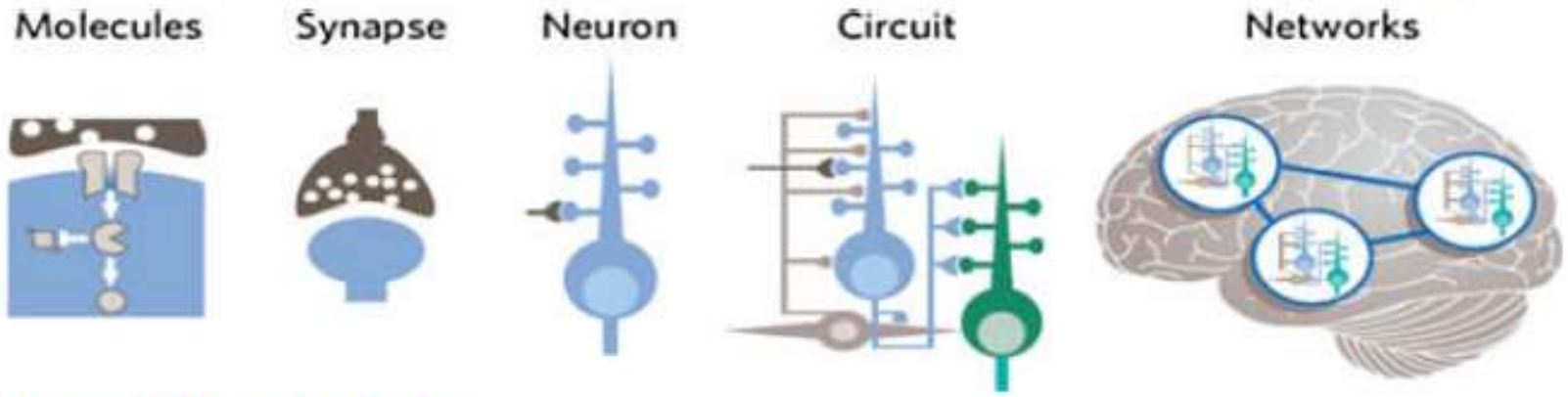
[redacted]¿Common underlying mechanisms?

Slow progression

Symptoms

Heterogeneous

No good correlation with pathology



Neurodegeneration

(Death, damage, dysfunction)

Clinical expression

Cell vulnerability factors

Cell defence systems

Trophic factors

Functional reserve

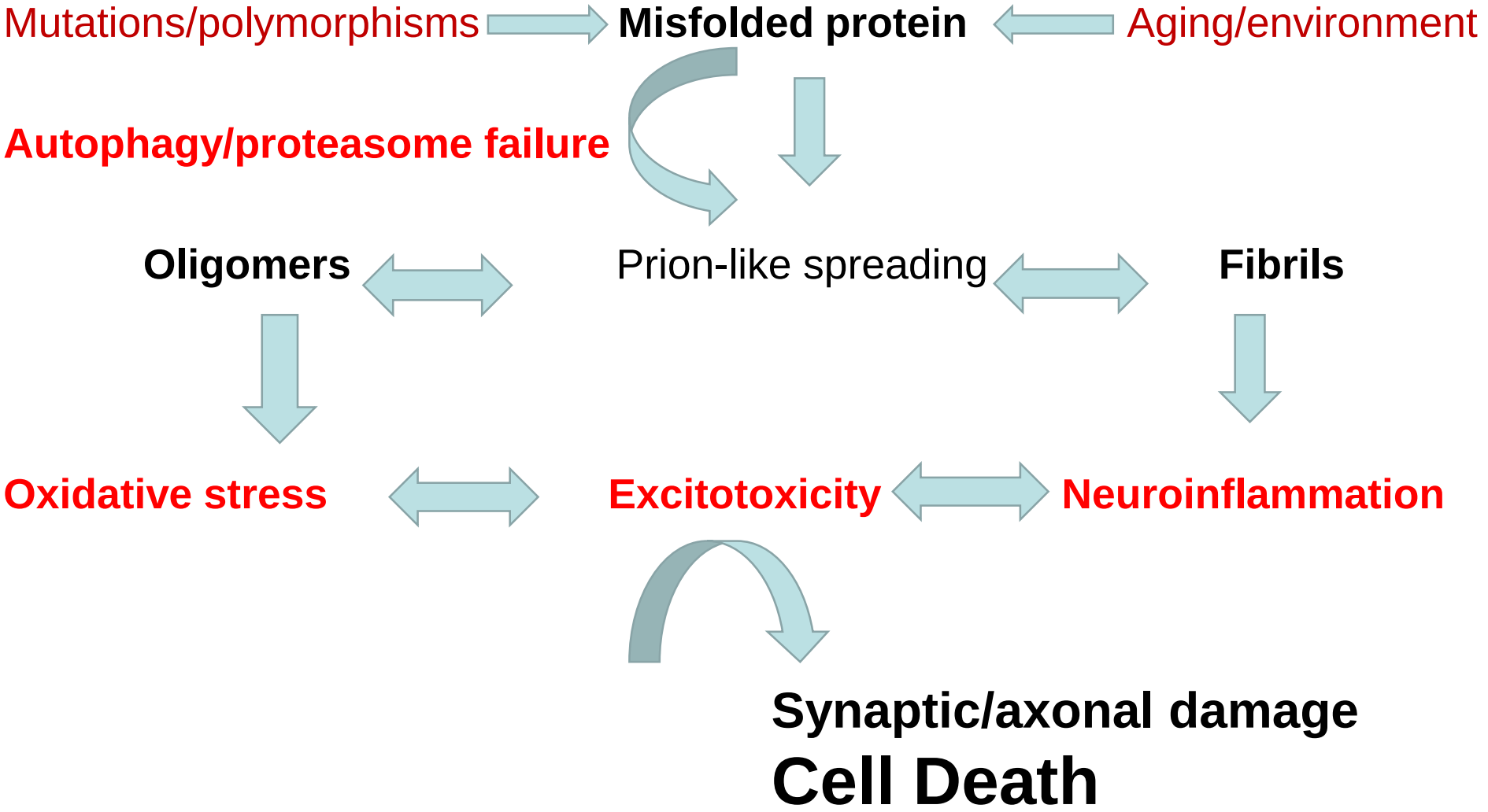
Compensatory mechanisms

Genes

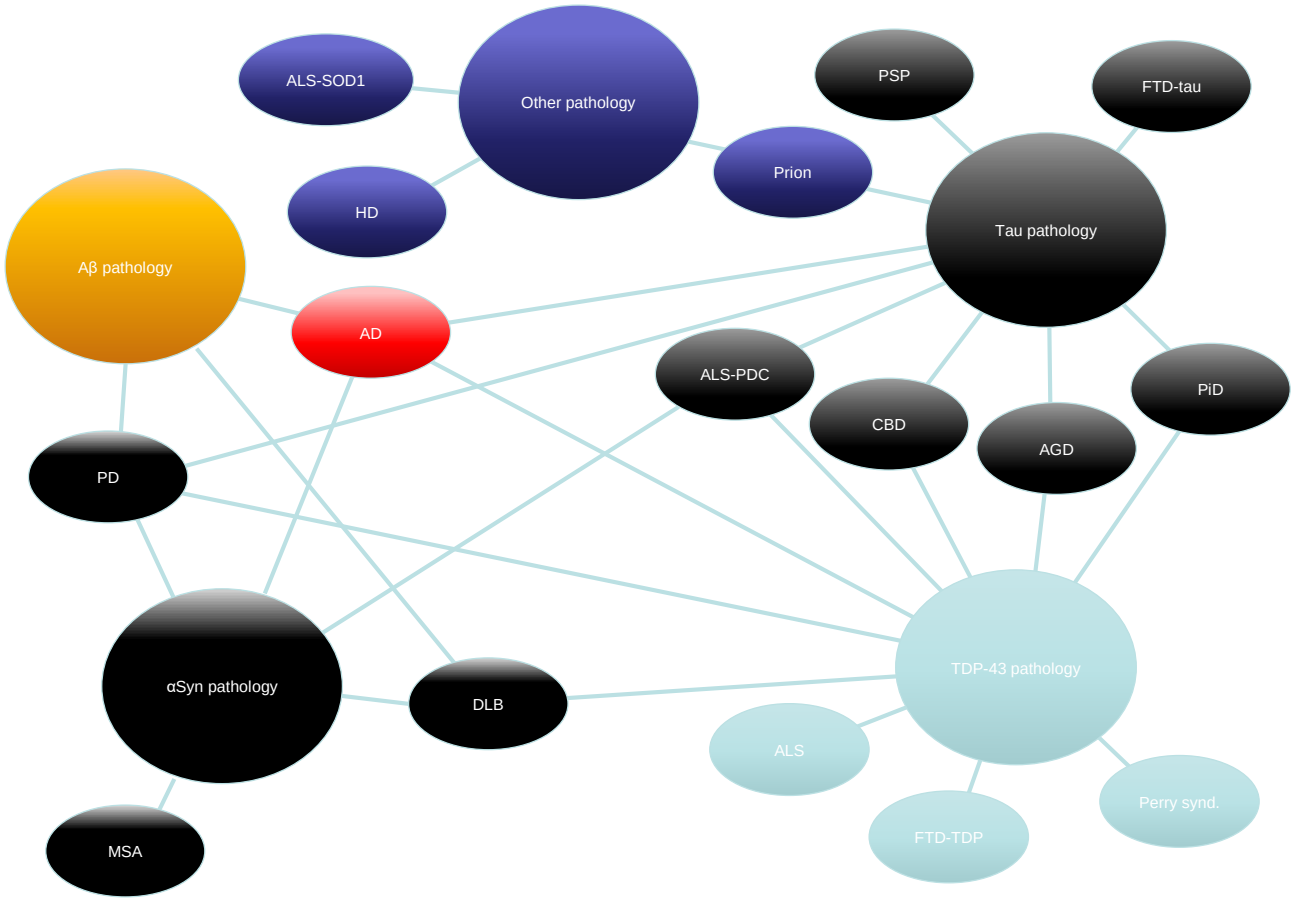
Aging

Associated lesions

Common pathogenetic mechanisms in neurodegenerative diseases



Interrelated neurodegenerative proteinopathies



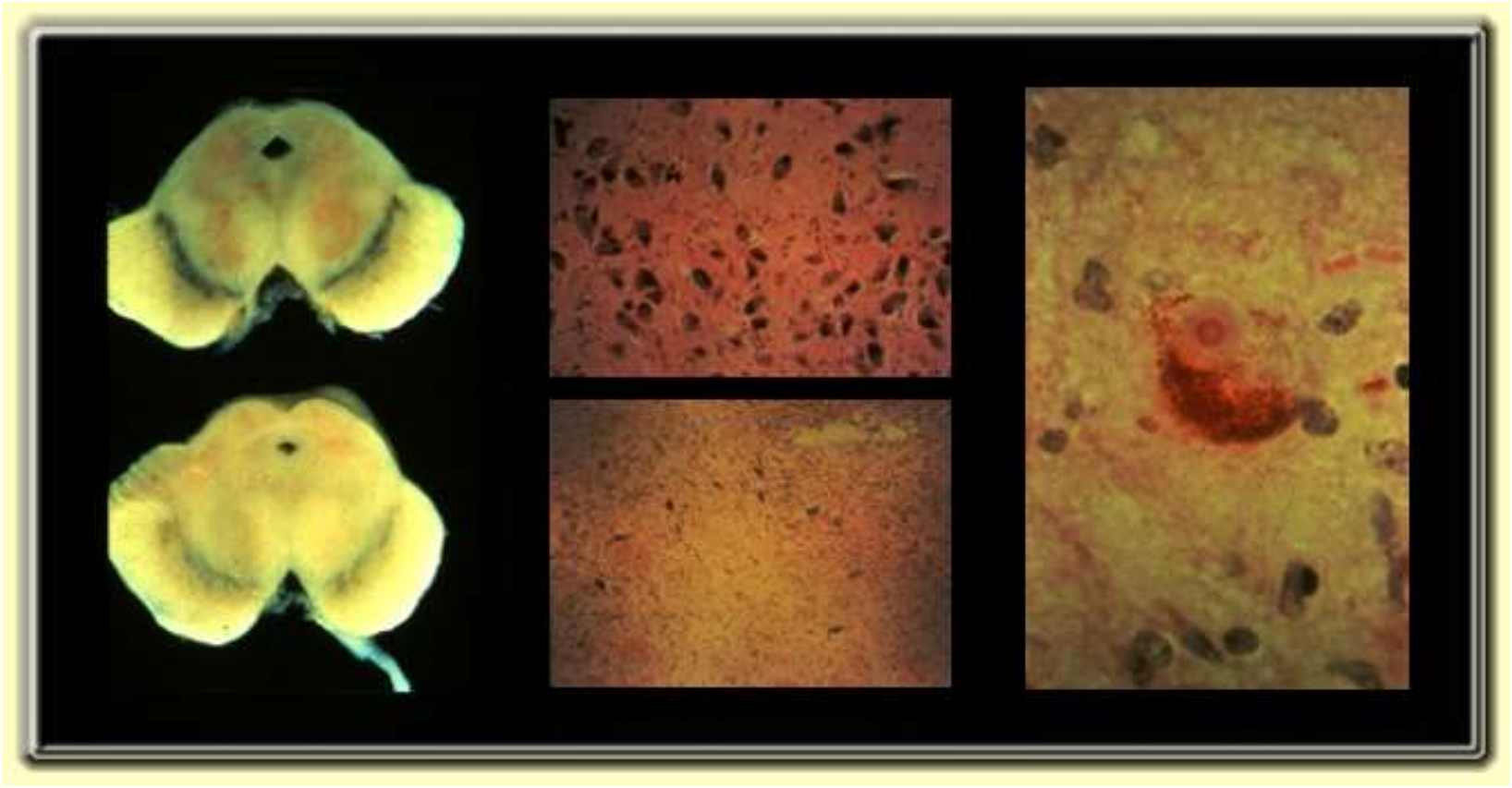
Schematic of the interrelated neurodegenerative proteinopathies. Diseases are organized in color blocks that indicate their primary proteinaceous aggregate. AD has primary proteinaceous aggregates of both Aβ (orange) and tau (dark green) and is designated red. Diseases are connected to proteinaceous aggregates that can be observed in at least some cases of the disease with lines

Image from: Golde TE, et al. J Clin Invest 2013;123:1847–1855

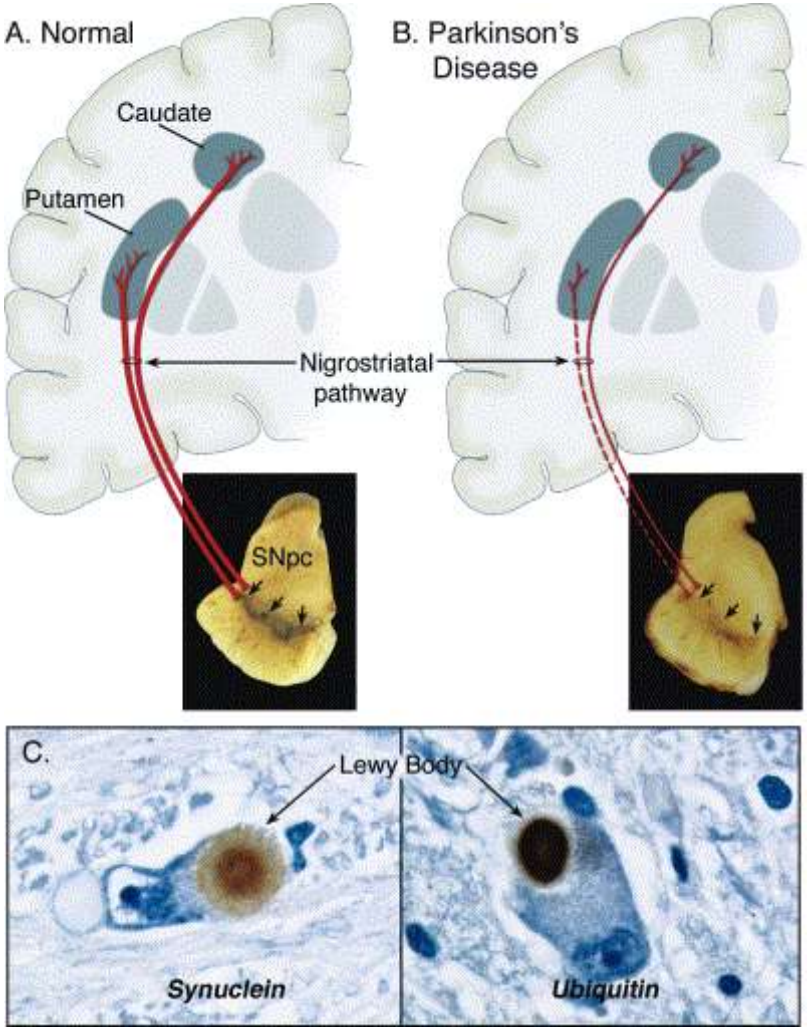
Aβ, amyloid beta; AD, Alzheimer's disease; AGD, argyrophilic grain disease; ALS, amyotrophic lateral sclerosis; αSyn, α-synuclein; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; HD, Huntington's disease; MSA, multiple system atrophy; Perry synd., Perry syndrome; PD, Parkinson's disease; PDC, Parkinsonism-dementia complex; PiD, Pick's disease; PSP, progressive supranuclear palsy; TDP-43, transactive response DNA binding protein

Golde TE, et al. J Clin Invest 2013;123:1847–1855

Pathology of Parkinson's disease



Disease hallmarks

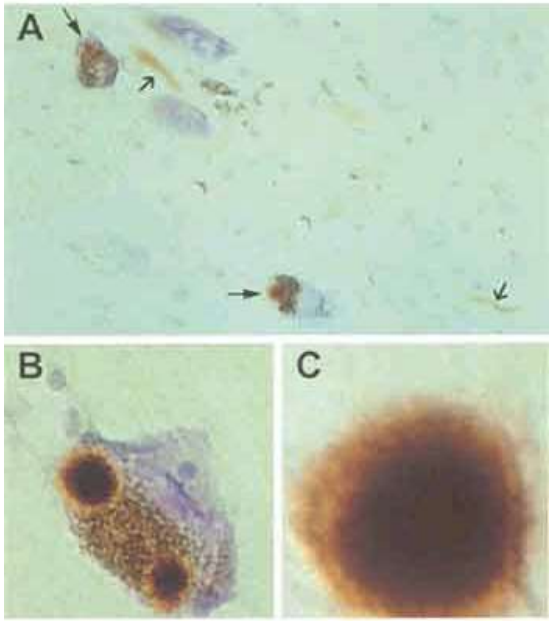


Dauer W. et al, Neuron, 2003

- Loss of dopamine-producing neurons in the substantia nigra pars compacta (SNpc).

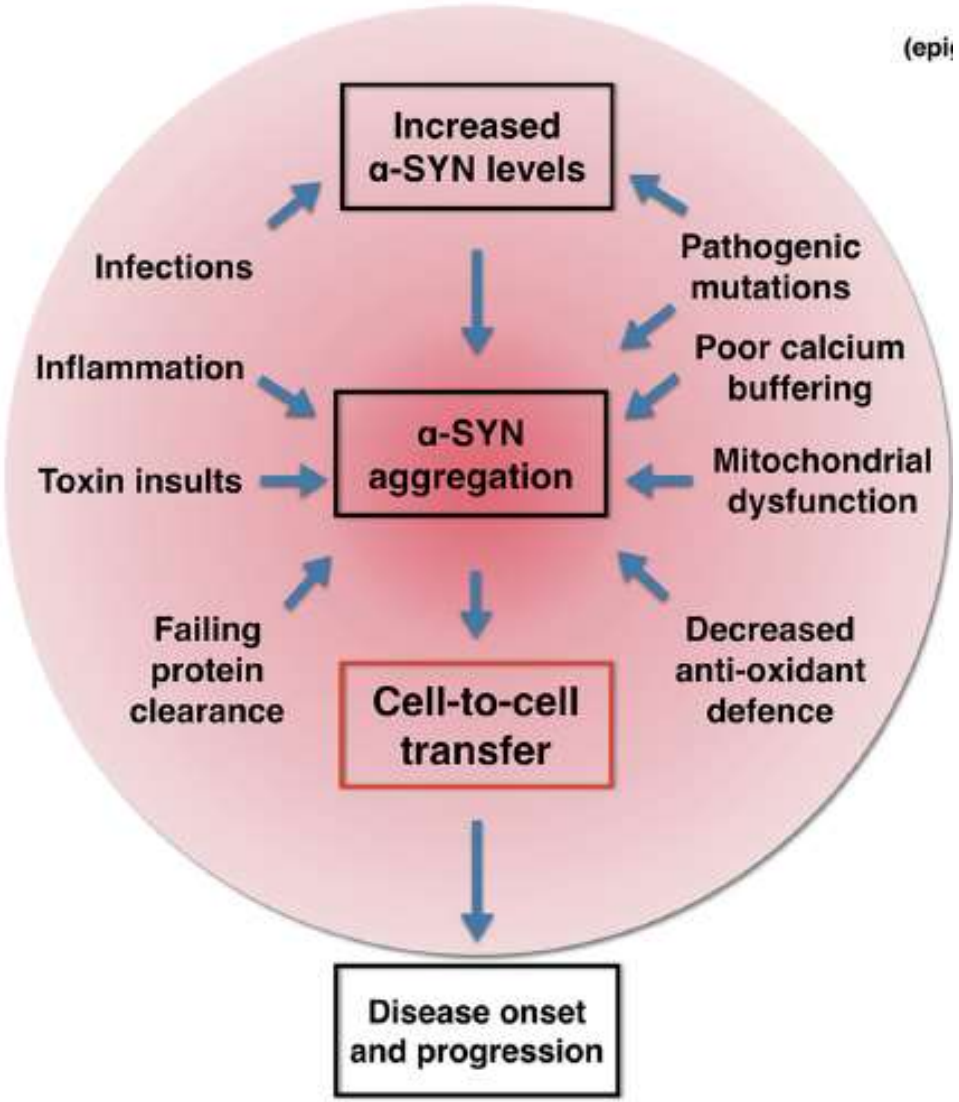
- Alpha-synuclein (aSN) enriched inclusions known as Lewy-Bodies.

Alpha-synuclein



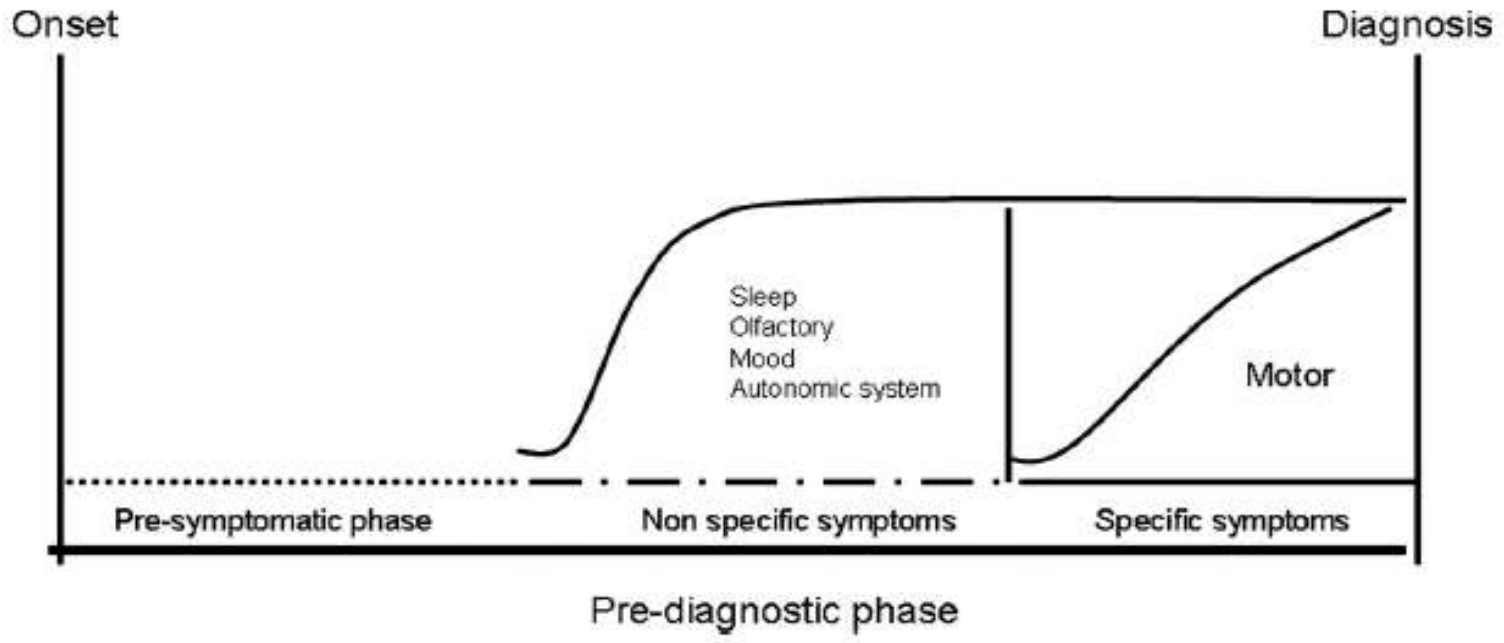
- Main constituent of Lewy bodies (LBs).
- Ubiquitously expressed, especially in presynaptic terminals.
- May aggregate and form insoluble fibrils in vitro and in vivo (LBs).
- SNCA gene mutations, multiplications as well as its increased expression due to its promoter variant (REP1), the exposure to toxic agents (oxidants, metals, pesticides), its decreased degradation may promote alpha-synuclein protein aggregation.

Prying into the Prion Hypothesis for Parkinson's Disease



The Journal of Neuroscience, October 11, 2017 • 37(41):9808–9818

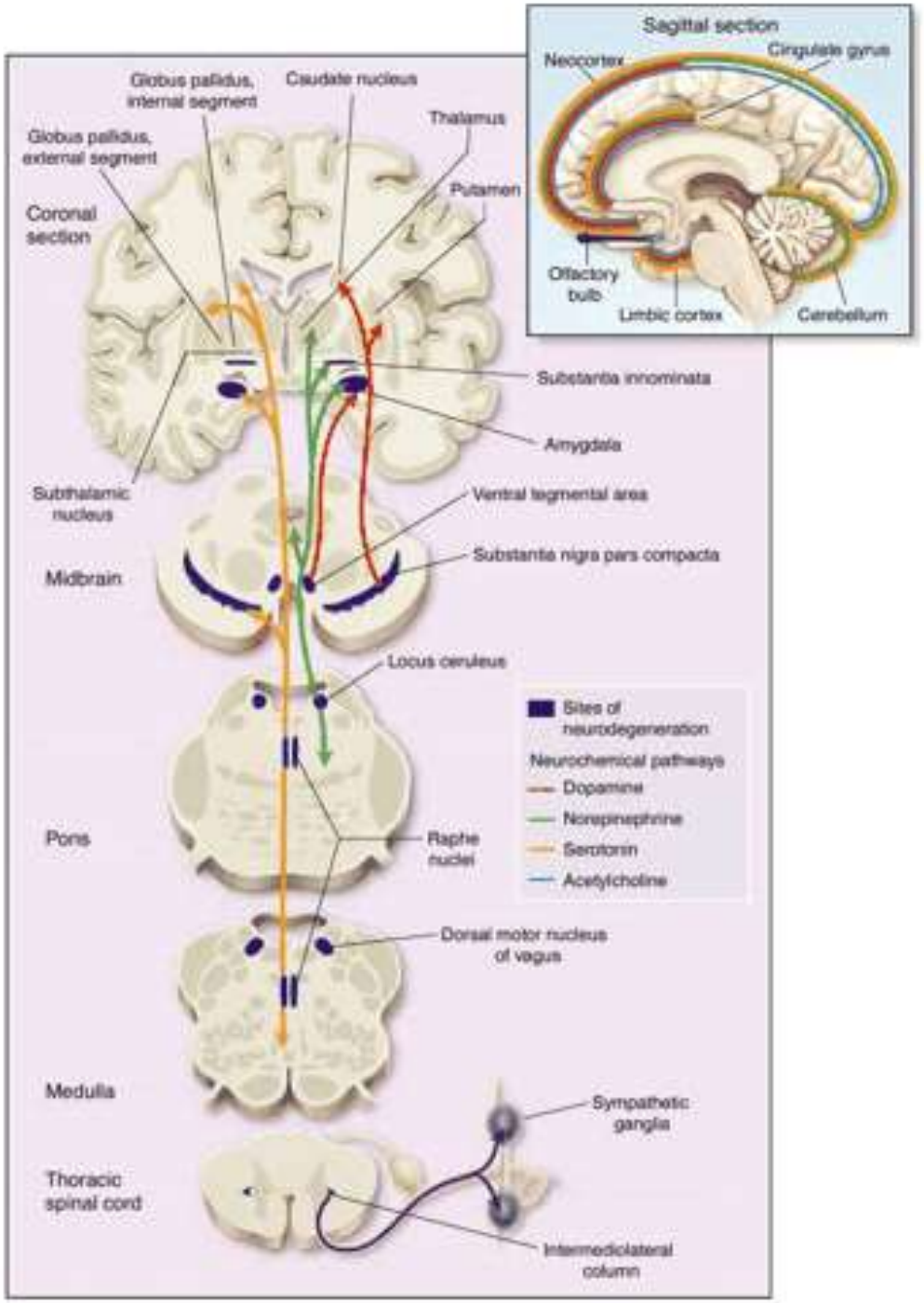
YEARS FROM DISEASE ONSET TO DIAGNOSIS



PD: widespread pathology

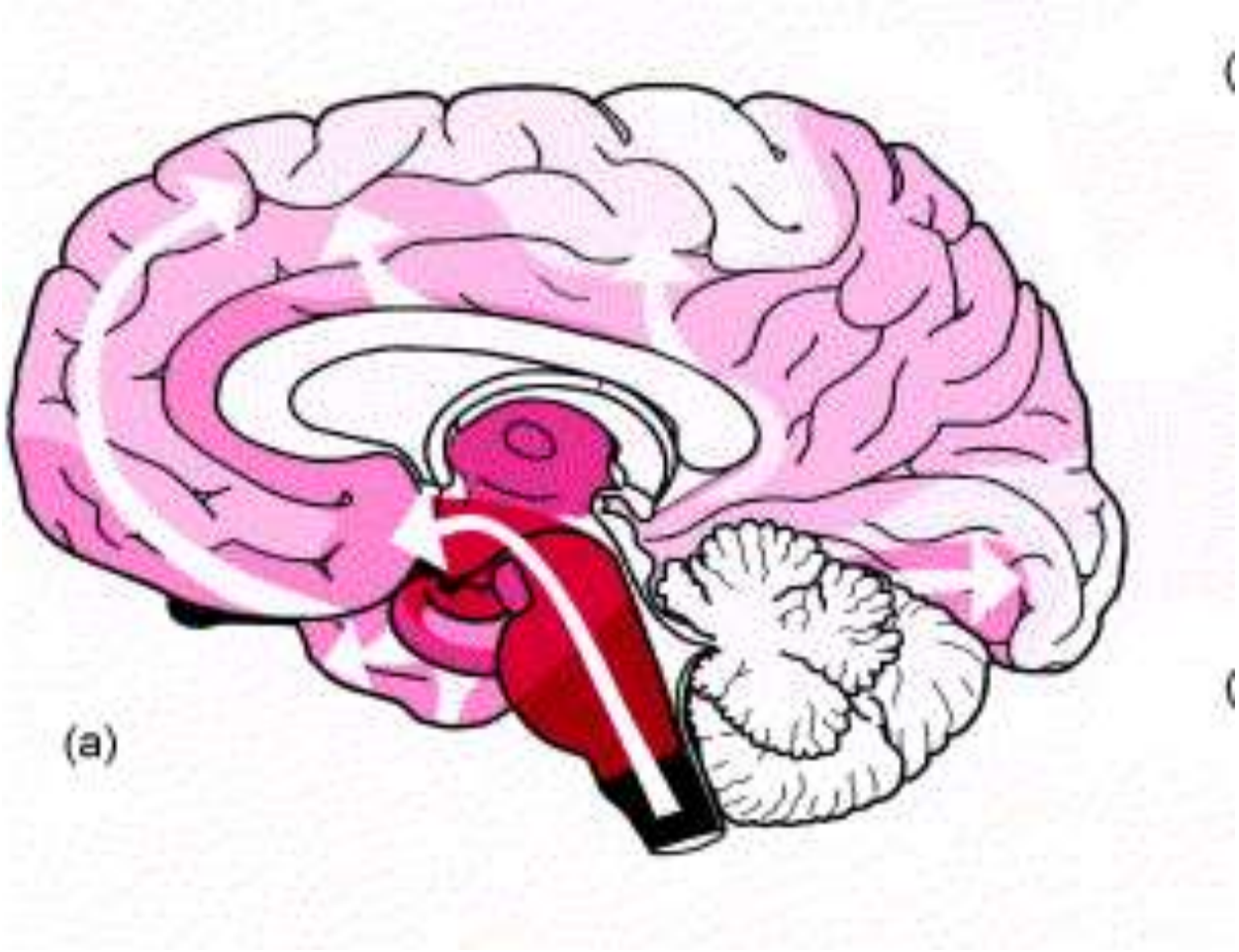
The Sites of Neurodegeneration and Neurochemical Pathways Involved in Parkinson's Disease.

The sites characterized by pathological changes in Parkinson's disease are dark blue (see the text for details). The neurochemical pathways that are affected by this disease are indicated by the colored arrows. The destinations of these pathways are indicated on the axial "sections" by the points of the arrows and on the sagittal section of the brain by colored outlining (red indicates dopamine; green, norepinephrine; orange, serotonin; and turquoise, acetylcholine).

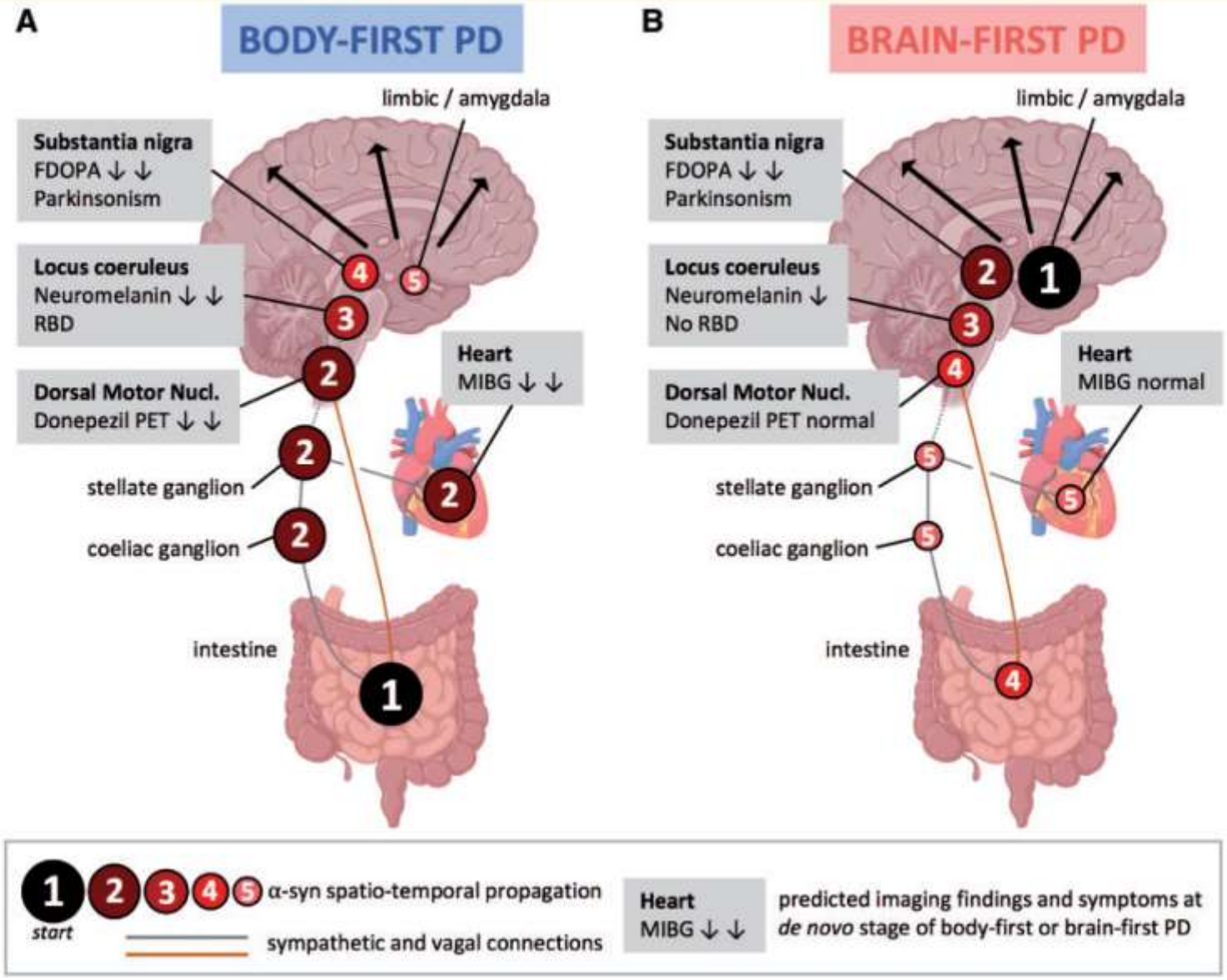


Lang a

Braak Stages



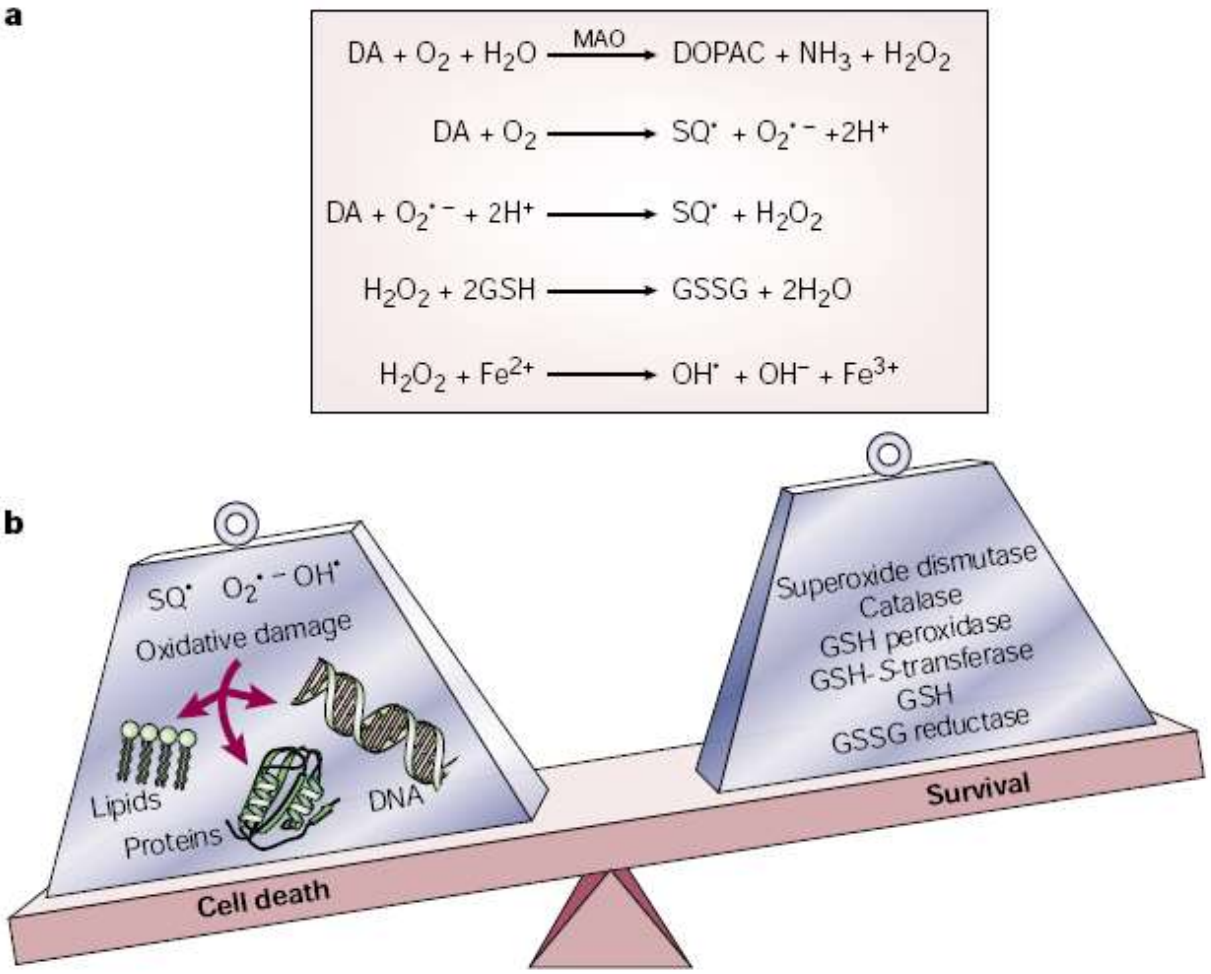
Braak, et al. Neurobiology of Aging 2003; 24:197-211

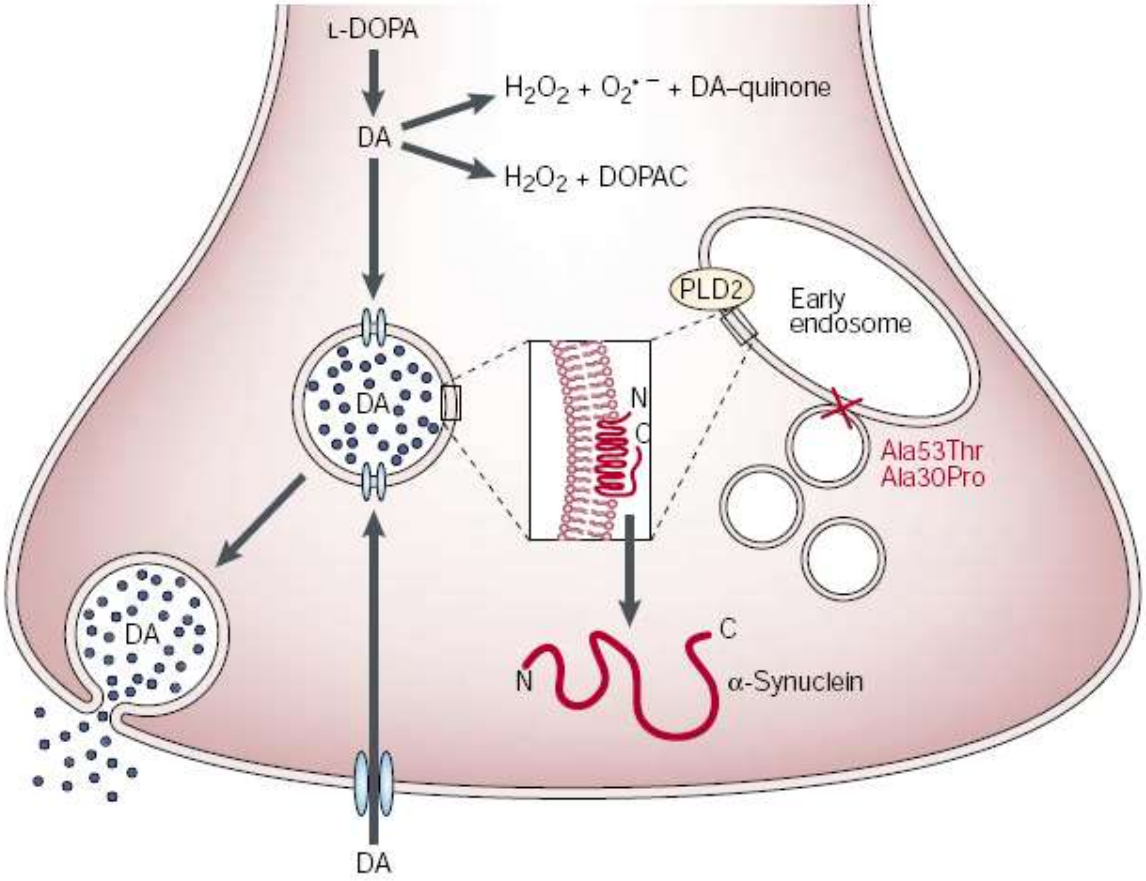

A
BODY-FIRST PD
limbic / amygdala
Substantia nigra
FDOPA ↓ ↓
Parkinsonism
Locus coeruleus
Neuromelanin ↓ ↓
RBD
Dorsal Motor Nucl.
Donepezil PET ↓ ↓
Heart
MIBG ↓ ↓
stellate ganglion
coeliac ganglion
intestine
B
BRAIN-FIRST PD
limbic / amygdala
Substantia nigra
FDOPA ↓ ↓
Parkinsonism
Locus coeruleus
Neuromelanin ↓
No RBD
Dorsal Motor Nucl.
Donepezil PET normal
Heart
MIBG normal
stellate ganglion
coeliac ganglion
intestine
start
α-syn spatio-temporal propagation
sympathetic and vagal connections
Heart
MIBG ↓ ↓
predicted imaging findings and symptoms at
de novo stage of body-first or brain-first PD

α-Synuclein induced degeneration

- Aggregation and fibrillation are thought to play a central role
  - Lead to a dysfunction in protein handling by inhibiting proteasome and autophagy
  - How mutations in α-synuclein cause selective degeneration of dopaminergic neurons, since α-synuclein is a ubiquitously expressed protein?
    - Oxidative ligation of dopamine to α-synuclein leads to the accumulation of the α-synuclein protofibril, which may be the toxic α-synuclein moiety

Oxidative stress and antioxidants




L-DOPA
DA
$H_2O_2 + O_2^{\bullet -}$ + DA–quinone
H_2O_2 + DOPAC
PLD2
Early endosome
DA
N
C
Ala53Thr
Ala30Pro
DA
C
N
α-Synuclein
DA

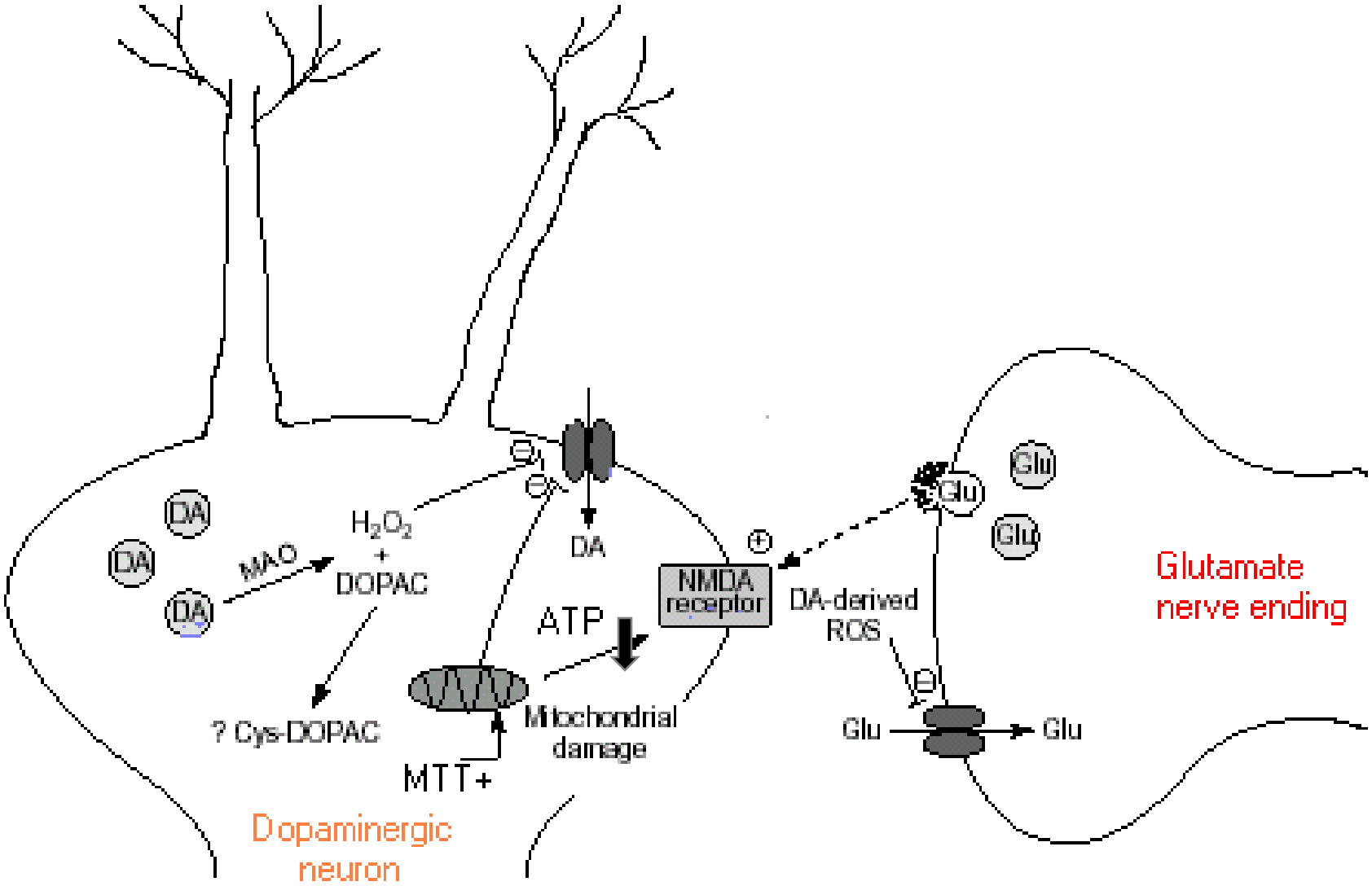
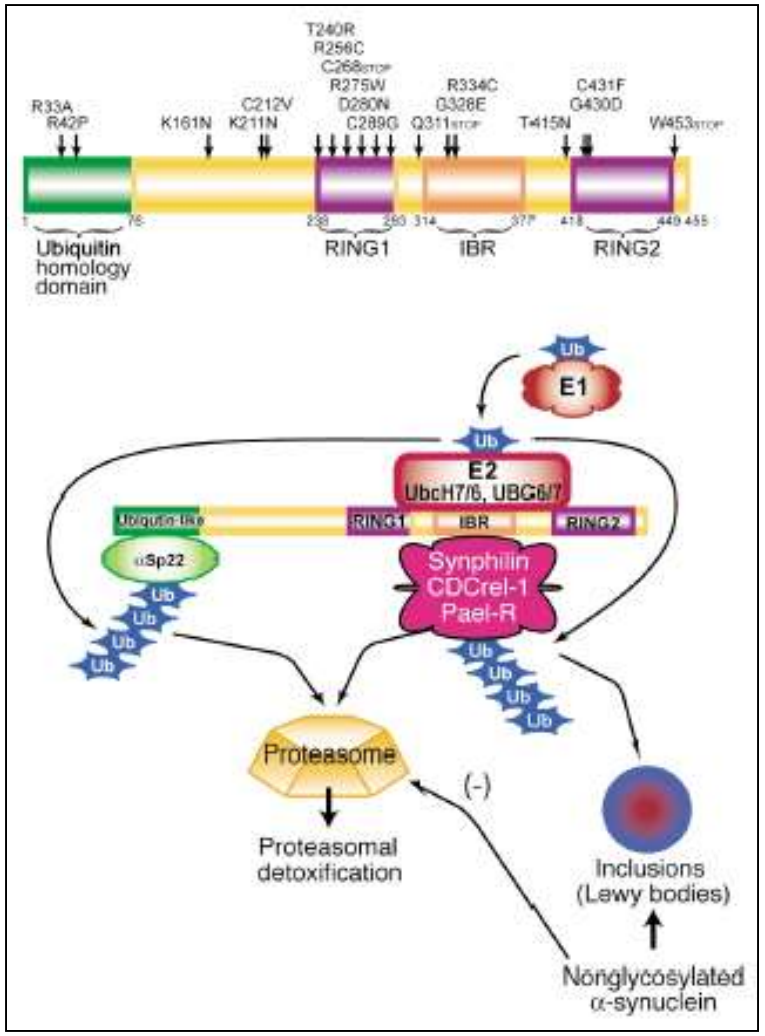

DA
DA
DA
MAO
H_2O_2
+
DOPAC
? Cys-DOPAC
DA
ATP
NMDA receptor
Mitochondrial damage
MTT+
Dopaminergic neuron
Glu
Glu
Glu
DA-derived ROS
Glu
Glu
Glutamate nerve ending

Table 1 | **Parkinson's disease-associated genes**

Locus	Gene	Inheritance	Function	Phenotype
*PARK1/4	α-Synuclein	Autosomal dominant	Involved in synaptic vesicle formation	Age of onset: 30–60 years Lewy bodies: ++
PARK2	Parkin	Autosomal recessive	An E3 ligase	Age of onset: ~30 years ‡Lewy bodies: –
PARK6	Phosphatase and tensin homologue (PTEN)-induced kinase 1 (*PINK1*)	Autosomal recessive	A mitochondrial kinase	Age of onset: 30–50 years Lewy bodies: ?
PARK7	Parkinson's disease (autosomal recessive, early onset) 7 (*DJ1*)	Autosomal recessive	Involved in oxidative stress response	Age of onset: 20–40 years Lewy bodies: ?
PARK8	Leucine-rich repeat kinase 2 (*LRRK2*)	Autosomal dominant	A protein kinase	Age of onset: 40–60 years Lewy bodies: + variable pathology
Unmapped	HtrA serine peptidase 2 (*HTRA2*, also known as *OMI*)	Autosomal dominant? Predisposition	A serine protease and/or involved in stress response	Age of onset: 44–70 years Lewy bodies: ?

*PARK1 and 4 share an entry because they have been shown to be caused by the same gene. ‡There has been one reported case of a parkin-positive patient with Lewy bodies. ++ Fulminant Lewy body pathology. + Lewy bodies present.

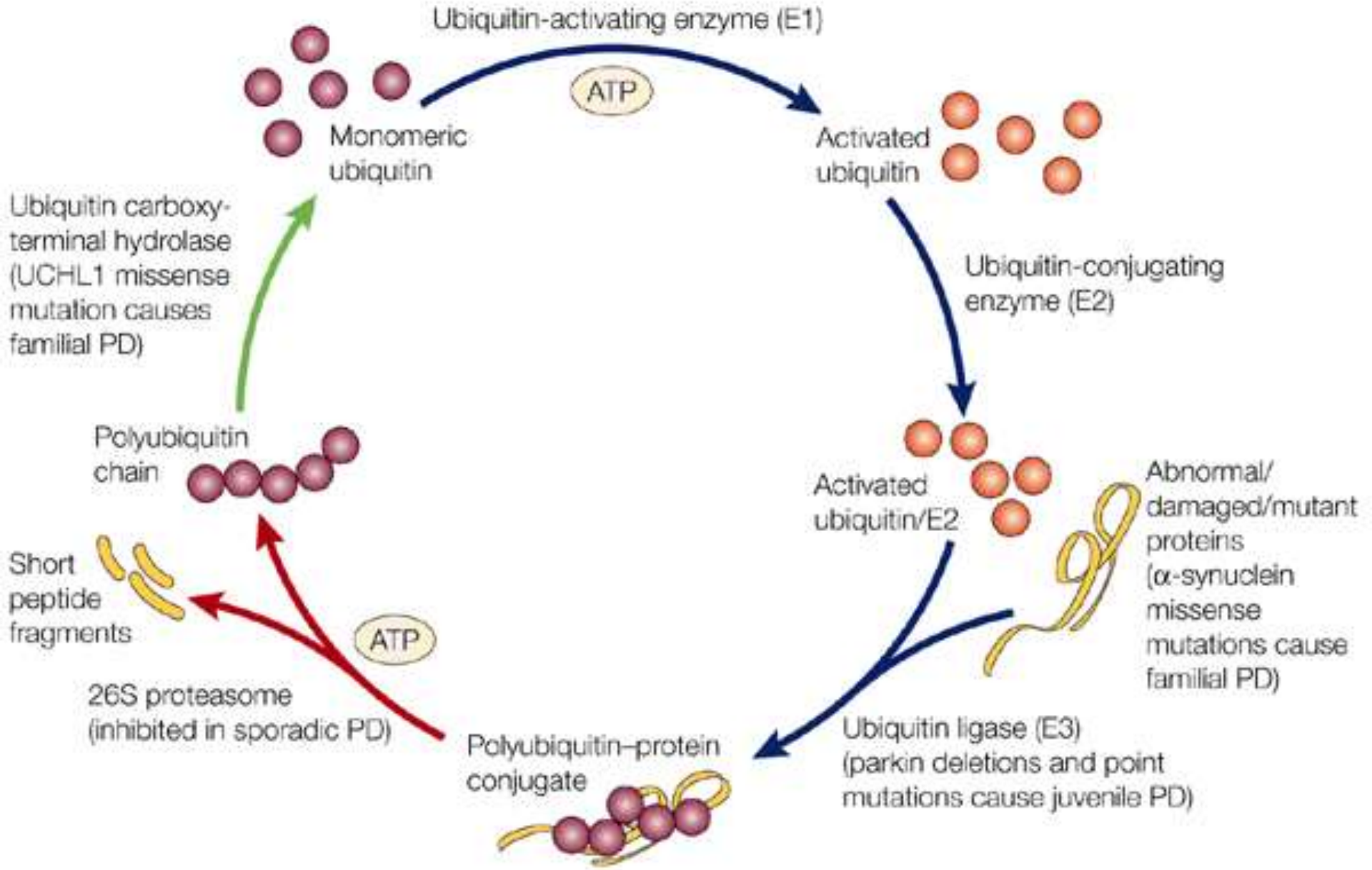
Parkin mutations



Structure of *parkin* and a model of parkin-mediated ubiquitination and its substrates

Top: Modular architecture of *parkin* and location of familial-associated disease-causing missense mutations. Disease-causing deletions, insertions, and frameshifts are not depicted.

Bottom: Model of *parkin*-mediated ubiquitination and Lewy body formation.


Ubiquitin-activating enzyme (E1)
ATP
Monomeric ubiquitin
Activated ubiquitin
Ubiquitin-conjugating enzyme (E2)
Ubiquitin carboxy-terminal hydrolase (UCHL1 missense mutation causes familial PD)
Polyubiquitin chain
Activated ubiquitin/E2
Abnormal/ damaged/mutant proteins (α-synuclein missense mutations cause familial PD)
Short peptide fragments
ATP
26S proteasome (inhibited in sporadic PD)
Polyubiquitin–protein conjugate
Ubiquitin ligase (E3) (parkin deletions and point mutations cause juvenile PD)

DJ-1 mutations

- Mutations of the DJ-1 gene cause parkinsonism probably through a loss of function
- Putative role in protecting neurons from oxidative stress
  - DJ-1 is a hydroperoxide-responsive protein that becomes more acidic following oxidative stress
  - In the presence of oxidative stress, wild-type DJ-1 translocates to the outer mitochondrial membrane and is associated with neuroprotection
    - This translocation is induced by oxidative post-translational modification of a key cysteine residue within the active site of DJ-1
    - It remains unclear how the mitochondrial translocation of DJ-1 confers protection, and this finding has yet to be confirmed for the endogenous protein

The Marsala kindred

Am. J. Hum. Genet. 68:000–000, 2001

Localization of a Novel Locus for Autosomal Recessive Early-Onset Parkinsonism, *PARK6*, on Human Chromosome 1p35-p36

Enza Maria Valente,[1,2] Anna Rita Bentivoglio,[1] Peter H. Dixon,[1] Alessandro Ferraris,[1] Tamara Ialongo,[1] Marina Frontali,[3] Alberto Albanese,[2,4] and Nicholas W. Wood[1]

[1]Department of Clinical Neurology, Institute of Neurology, London; [2]Department of Neurology, Catholic University, and [3]Institute of Experimental Medicine, CNR, Rome; and [4]National Neurological Institute "Carlo Besta", Milan

The cause of Parkinson disease (PD) is still unknown, but genetic factors have recently been implicated in the etiology of the disease. So far, four loci responsible for autosomal dominant PD have been identified. Autosomal recessive juvenile parkinsonism (ARJP) is a clinically and genetically distinct entity; typical PD features are associated with early onset, sustained response to levodopa, and early occurrence of levodopa-induced dyskinesias, which are often severe. To date, only one ARJP gene, *Parkin*, has been identified, and multiple mutations have been detected both in families with autosomal recessive parkinsonism and in sporadic cases. The *Parkin*-associated phenotype is broad, and some cases are indistinguishable from idiopathic PD. In >50% of families with ARJP that have been analyzed, no mutations could be detected in the *Parkin* gene. We identified a large Sicilian family with four definitely affected members (the Marsala kindred). The phenotype was characterized by early-onset (range 32–48 years) parkinsonism, with slow progression and sustained response to levodopa. Linkage of the disease to the *Parkin* gene was excluded. A genomewide homozygosity screen was performed in the family. Linkage analysis and haplotype construction allowed identification of a single region of homozygosity shared by all the affected members, spanning 12.5 cM on the short arm of chromosome 1. This region contains a novel locus for autosomal recessive early-onset parkinsonism, *PARK6*. A maximum LOD score 4.01 at recombination fraction .00 was obtained for marker *D1S199*.

PINK1 Mutations Are Associated with Sporadic Early-Onset Parkinsonism

Enza Maria Valente, MD, PhD,[1] Sergio Salvi, BSc,[1] Tamara Ialongo, MD,[2] Roberta Marongiu, BSc,[1] Antonio Emanuele Elia, MD,[2] Viviana Caputo, BSc,[1,3] Luigi Romito, MD,[4] Alberto Albanese, MD,[2,4] Bruno Dallapiccola, MD,[1,5] and Anna Rita Bentivoglio, MD, PhD[2]

We have recently reported homozygous mutations in the *PINK1* gene in three consanguineous families with early-onset parkinsonism (EOP) linked to the PARK6 locus. To further evaluate the pathogenic role of PINK1 in EOP and to draw genotype–phenotype correlates, we performed PINK1 mutation analysis in a cohort of Italian EOP patients, mostly sporadic, with onset younger than 50 years of age. Seven of 100 patients carried missense mutations in PINK1. Two patients had two PINK1 mutations, whereas in five patients only one mutation was identified. Age at onset was in the fourth-fifth decade (range, 37–47 years). The clinical picture was characterized by a typical parkinsonian phenotype with asymmetric onset and rare occurrence of atypical features. Slow progression and excellent response to levodopa were observed in all subject. Two of 200 healthy control individuals also carried one heterozygous missense mutation. The identification of a higher number of patients (5%) than controls (1%) carrying a single heterozygous mutation, along with previous positron emission tomography studies demonstrating a preclinical nigrostriatal dysfunction in PARK6 carriers, supports the hypothesis that haploinsufficiency of PINK1, as well as of other EOP genes, may represent a susceptibility factor toward parkinsonism. However, the pathogenetic significance of heterozygous PINK1 mutations still remains to be clarified.

Ann Neurol 2004;56:336–341

Hereditary Early-Onset Parkinson's Disease Caused by Mutations in *PINK1*

Enza Maria Valente,[1]*‡ Patrick M. Abou-Sleiman,[2]* Viviana Caputo,[1,3]† Miratul M. K. Muqit,[2,4]† Kirsten Harvey,[5] Suzana Gispert,[6] Zeeshan Ali,[6] Domenico Del Turco,[7] Anna Rita Bentivoglio,[9] Daniel G Healy,[2] Alberto Albanese,[10] Robert Nussbaum,[11] Rafael González-Maldonado,[12] Thomas Deller,[7] Sergio Salvi,[1] Pietro Cortelli,[13] William P. Gilks,[2] David S. Latchman,[4,14] Robert J. Harvey,[5] Bruno Dallapiccola,[1,3] Georg Auburger,[8]‡ Nicholas W. Wood[2]‡

Parkinson's disease (PD) is a neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the substantia nigra. We previously mapped a locus for a rare familial form of PD to chromosome 1p36 (PARK6). Here we show that mutations in *PINK1* (PTEN-induced kinase 1) are associated with PARK6. We have identified two homozygous mutations affecting the PINK1 kinase domain in three consanguineous PARK6 families: a truncating nonsense mutation and a missense mutation at a highly conserved amino acid. Cell culture studies suggest that PINK1 is mitochondrially located and may exert a protective effect on the cell that is abrogated by the mutations, resulting in increased susceptibility to cellular stress. These data provide a direct molecular link between mitochondria and the pathogenesis of PD.

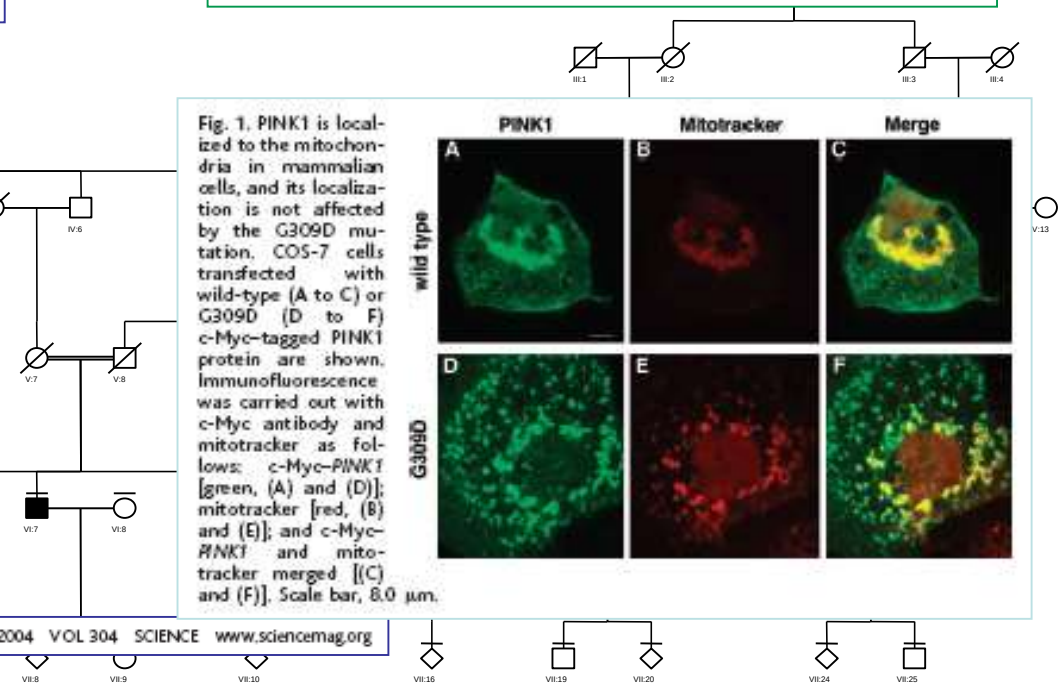


Fig. 1. PINK1 is localized to the mitochondria in mammalian cells, and its localization is not affected by the G309D mutation. COS-7 cells transfected with wild-type (A to C) or G309D (D to F) c-Myc–tagged PINK1 protein are shown. Immunofluorescence was carried out with c-Myc antibody and mitotracker as follows: c-Myc–*PINK1* [green, (A) and (D)]; mitotracker [red, (B) and (E)]; and c-Myc–*PINK1* and mitotracker merged [(C) and (F)]. Scale bar, 8.0 μm.

21 MAY 2004 VOL 304 SCIENCE www.sciencemag.org

PINK1 and mitochondria

- Both wild-type and mutant PINK1 proteins primarily locate to the mitochondrion
- In cell culture, wild-type PINK1 seems to protect cells from stress-induced mitochondrial dysfunction as well as stress induced apoptosis
- The *PINK1* gene provides a direct molecular link between mitochondria and PD, formerly suspected from indirect evidence

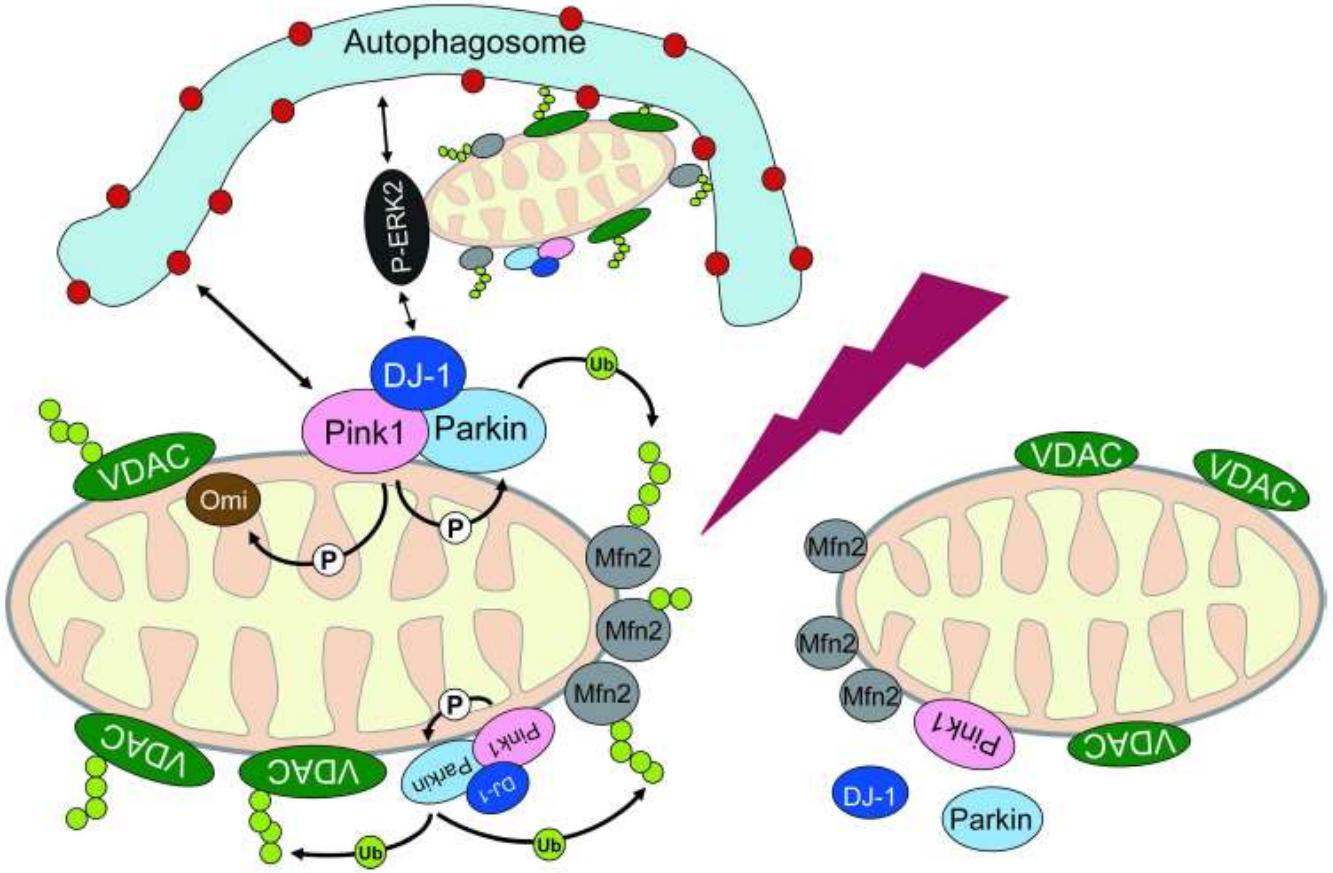
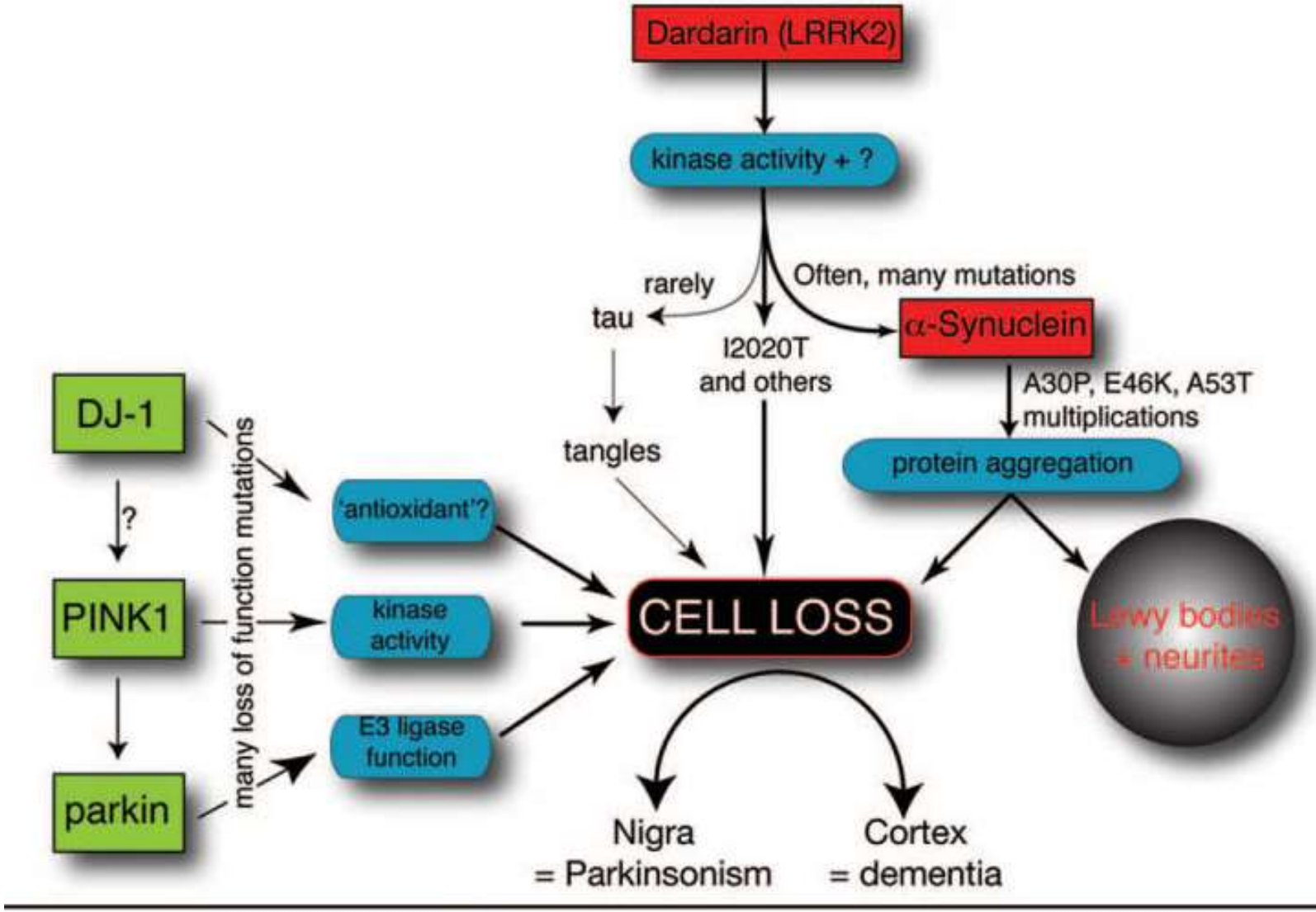


Figure 3: Model of mitochondrial clearance mechanisms controlled by PD-associated genes PINK1, Parkin, DJ-1 and Omi/HtrA2.

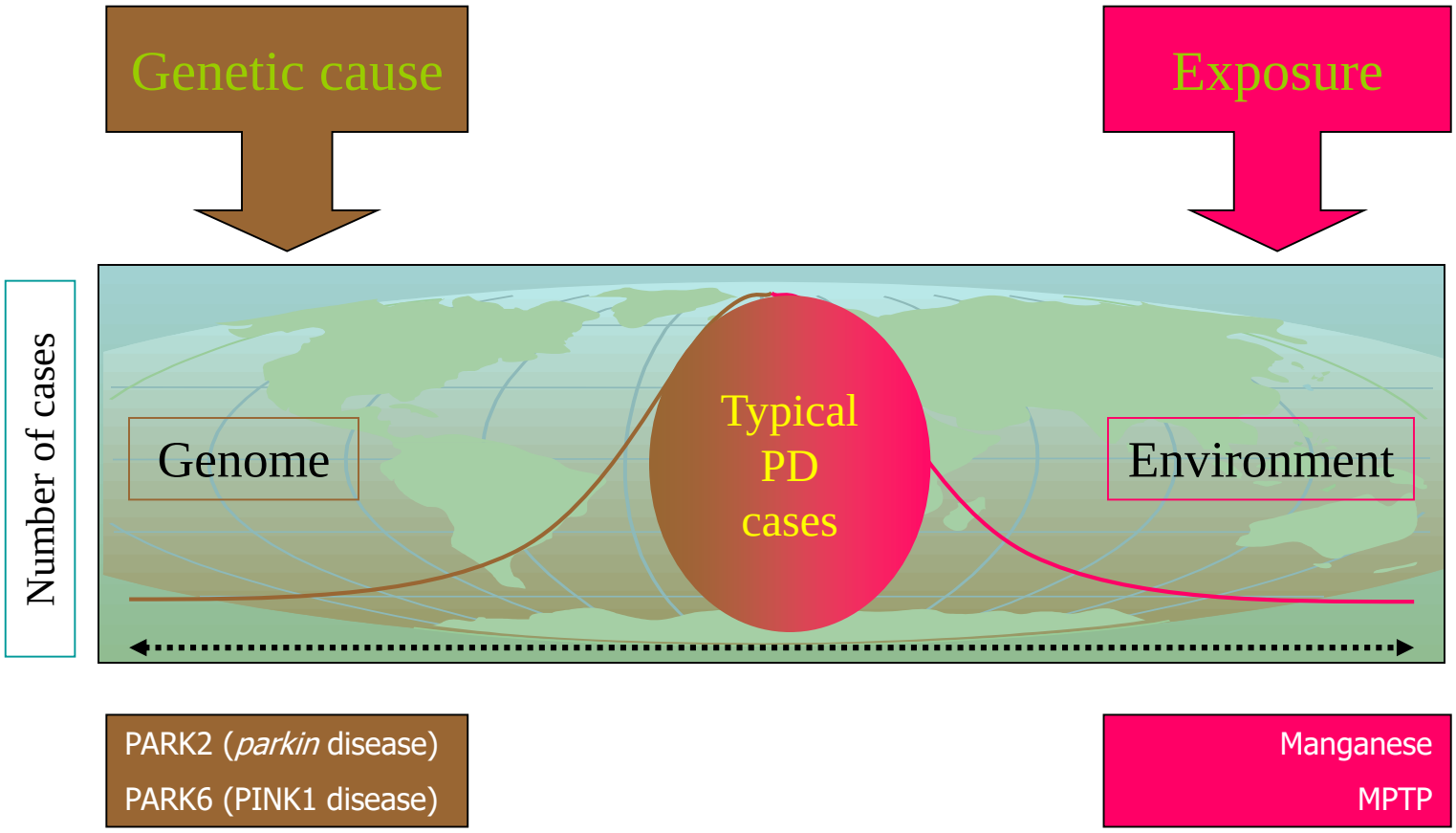
The PD-associated genes PINK1 (pink), Parkin (light blue), DJ-1 (dark blue), and Omi/HtrA2 (brown) are known to influence mitophagy. Under stress condition PINK-1 is thought to be stabilized at the outer membrane of dysfunctional mitochondria (left). By phosphorylation it could modulate the activity of the mitochondrial serine protease Omi/HtrA2 and/or Parkin, the latter in response being recruited to mitochondria. Moreover PINK1 has been reported to directly interact with the autophagic marker protein LC-3 (red). Parkin was shown to regulate the abundance of the mitochondrial fusion protein mitofusin 2 (Mfn2; grey) at the outer membrane by ubiquitination (light green), thereby inhibiting mitochondrial fusion events in Drosophila. In a mammalian model Parkin was shown to ubiquitinate the outer mitochondrial membrane protein VDAC (dark green) to mark dysfunctional mitochondria for subsequent p62-mediated recruitment to the autophagosome. DJ-1 may be involved in the regulation of mitochondrial p-ERK2 (black), thereby promoting the clearance of dysfunctional mitochondria by the autophagosome.

250x165mm (300 x 300 DPI)

LOSS AND GAIN OF FUNCTIONS

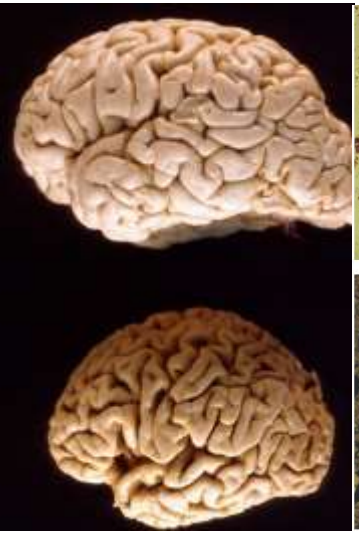


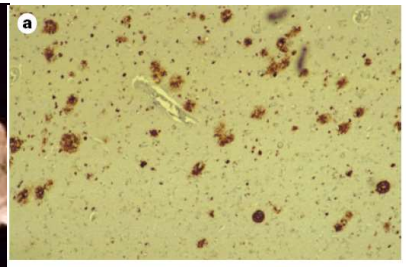
Parkinson's disease

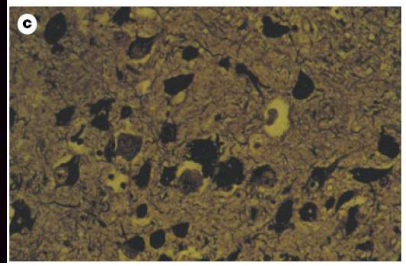


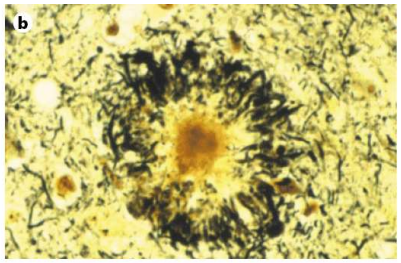
Alzheimer disease: clinical-pathological construct

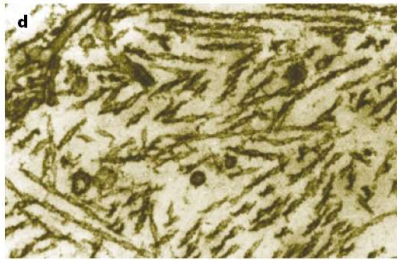
A. Alzheimer, 1906









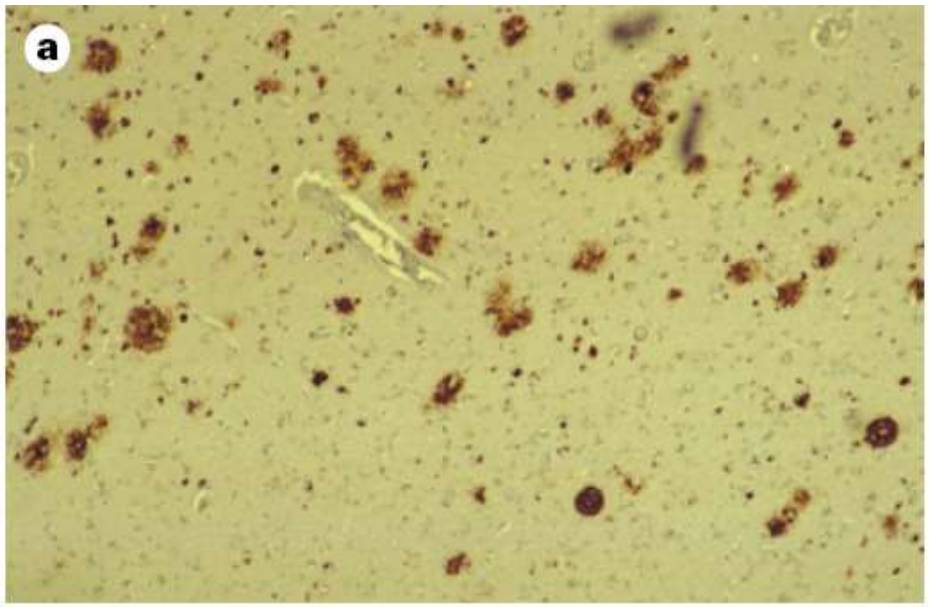


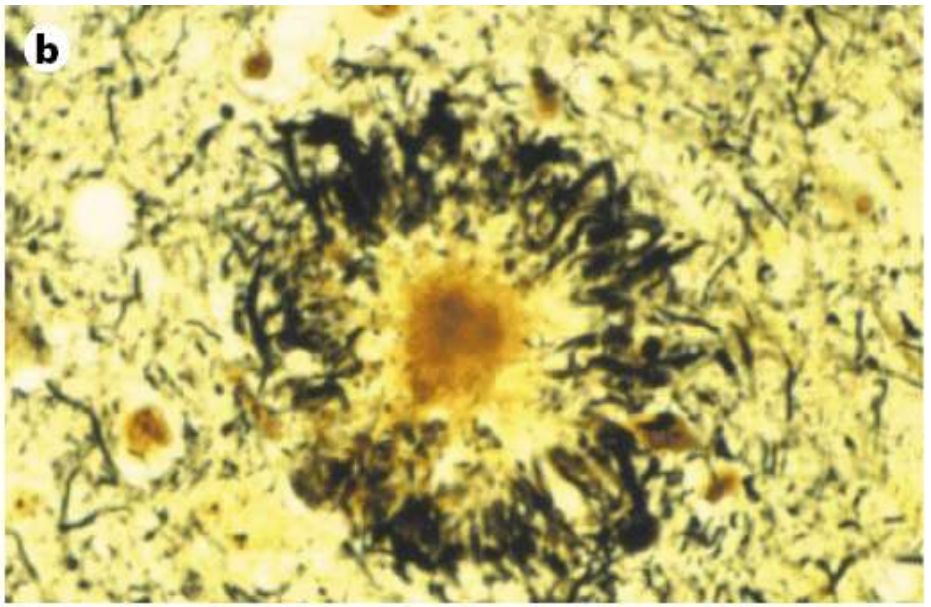
Brain atrophy
Senile Plaques
Neurofibrillary tangles

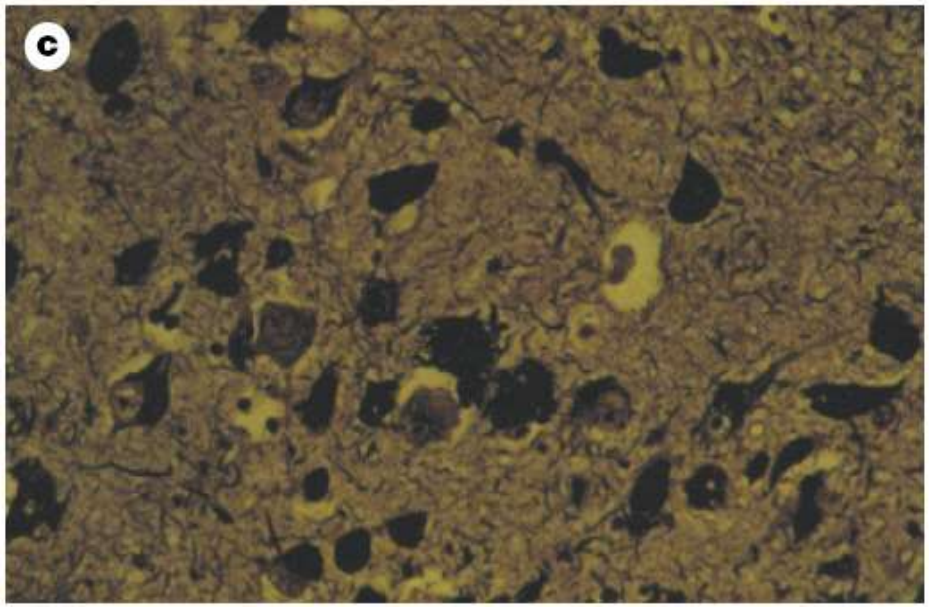
Presenile dementia

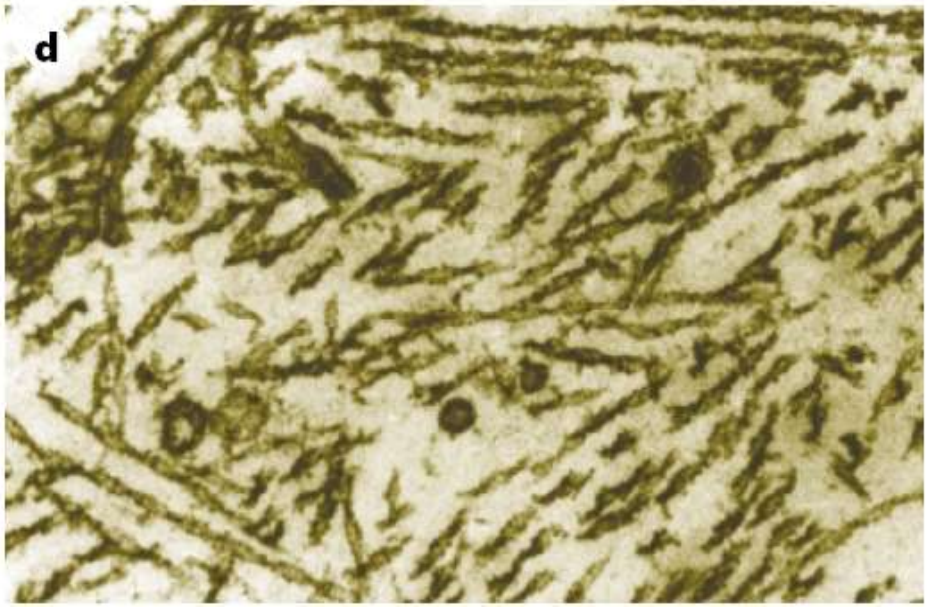
In vivo diagnosis is only «probable», certainty is by autopsy

AD pathological hallmarks

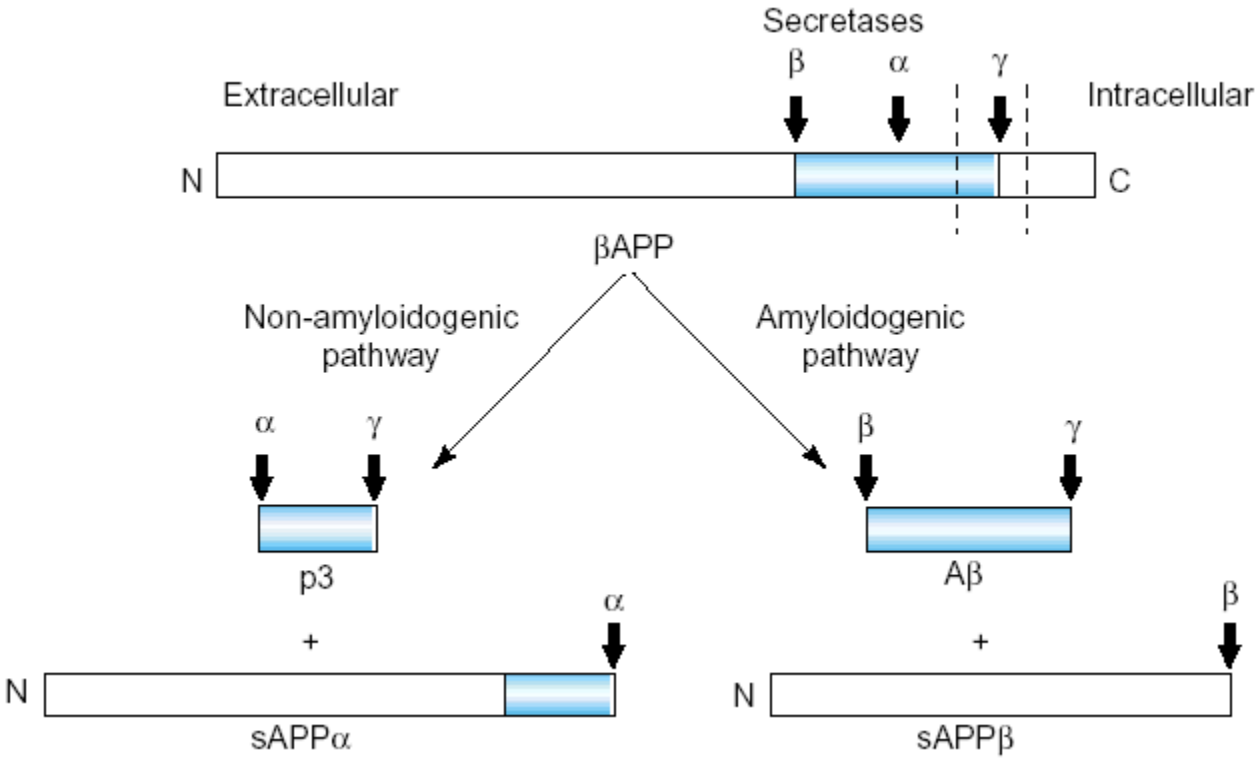




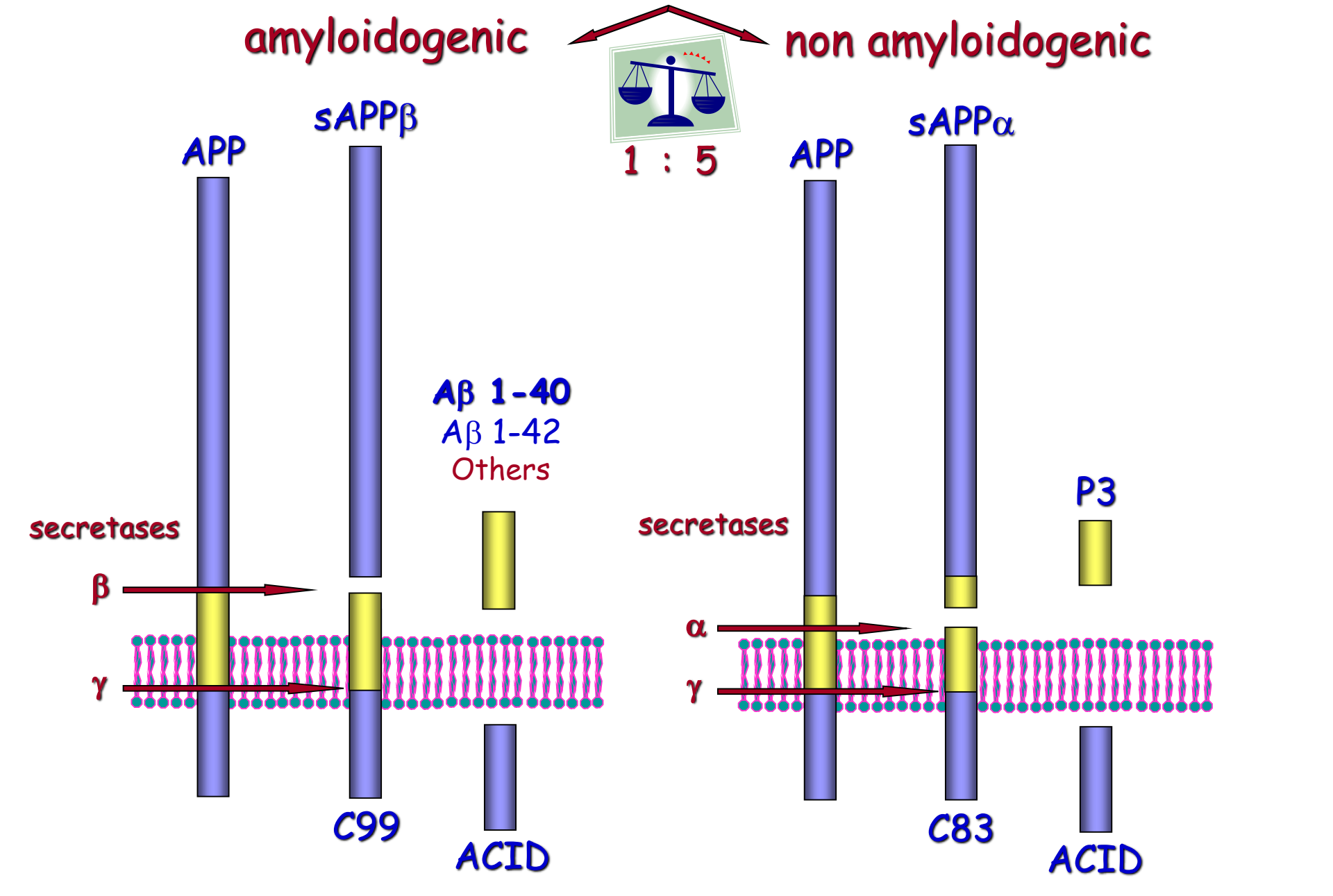




Proteolytic processing of β-amyloid (Aβ) precursor protein βAPP.



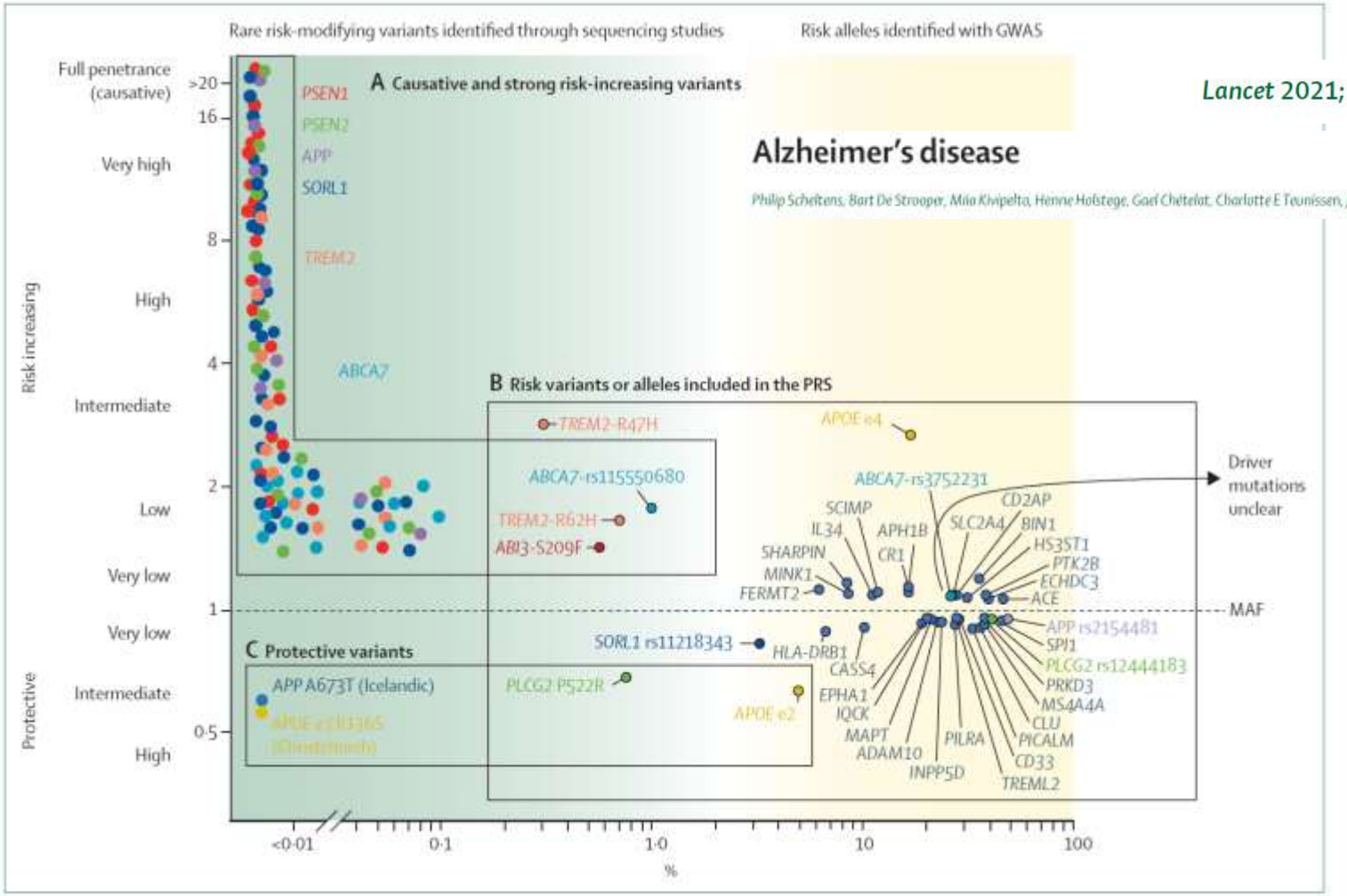
APP Processing



Genetic evidence for the primary role of Abeta

- Dose effect of Abeta production in Down syndrome
- Increased Abeta production in mutations of APP, PS1, PS2 and SORL1 genes
- Decreased Abeta production in protective APP A673T mutation (decreased BACE activity)
- Most genetic risk factors interact with Abeta processing and pathways

(Nat Genetics, Dec 2013 Meta-analysis of 74.000 individuals)



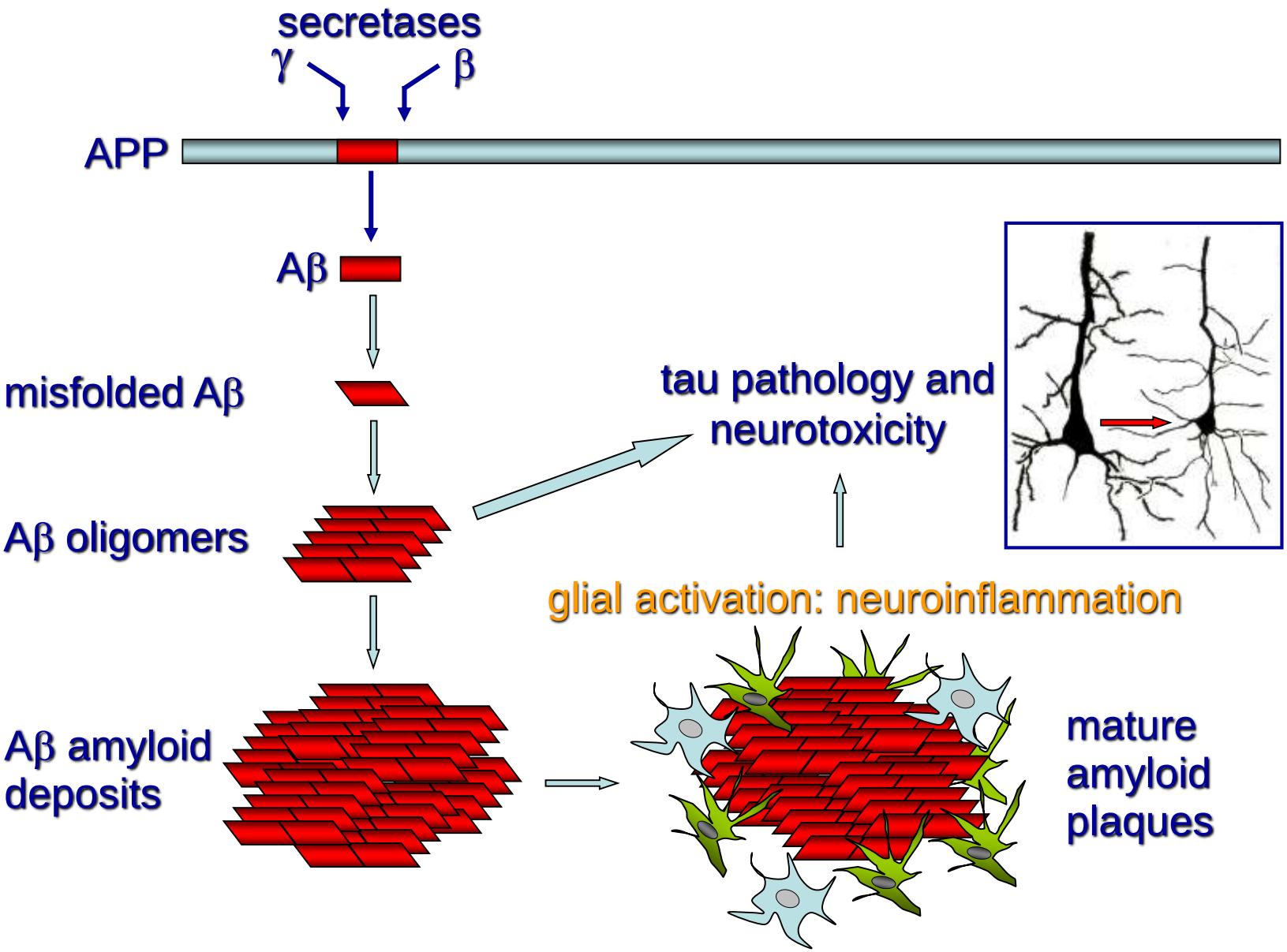
Alzheimer's disease

Philip Scheltens, Bart De Strooper, Miia Kivipelto, Henne Holstege, Gael Chételat, Charlotte E Teunissen, Jeffrey Cummings, Wiesje M van der Flier

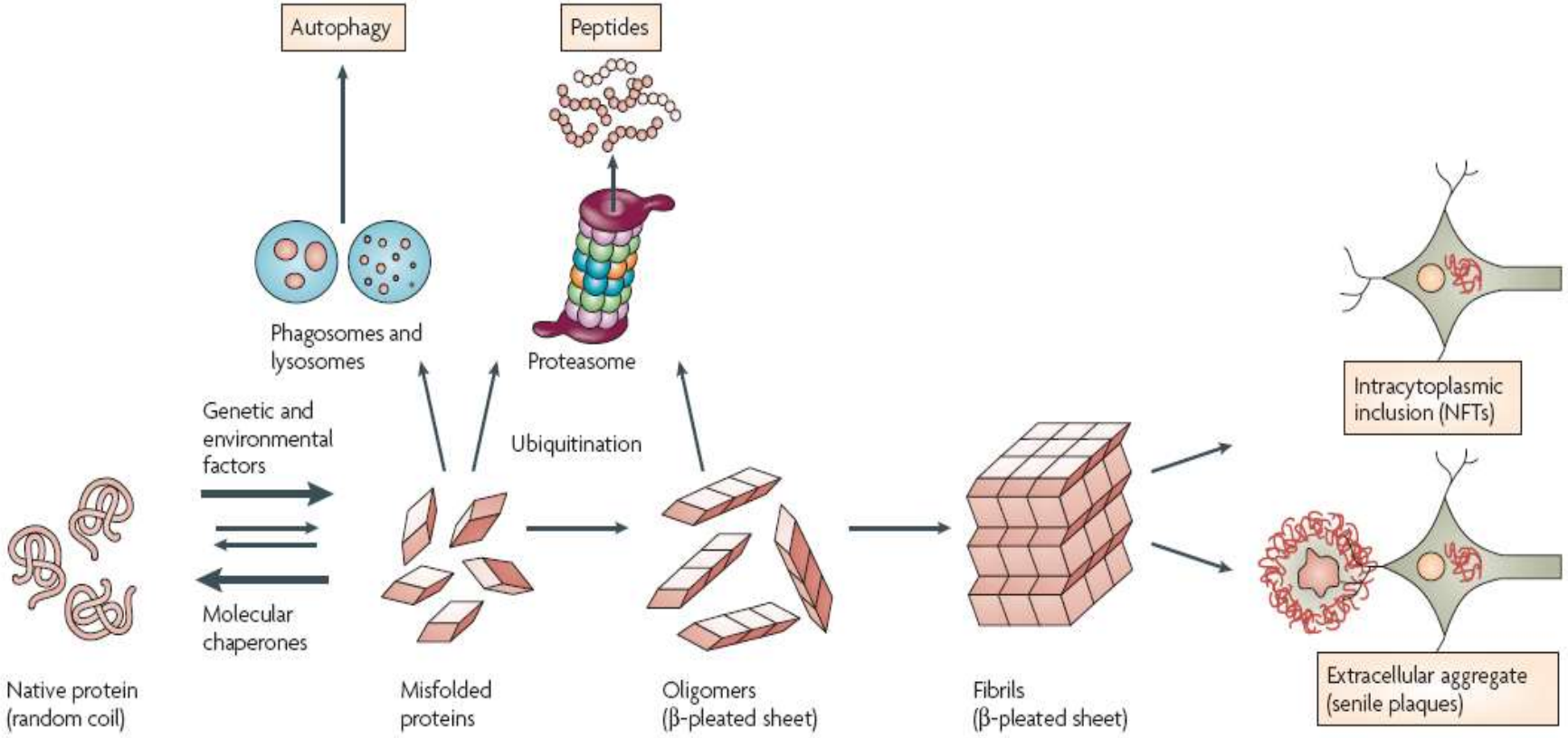
Lancet 2021; 397: 1577–90

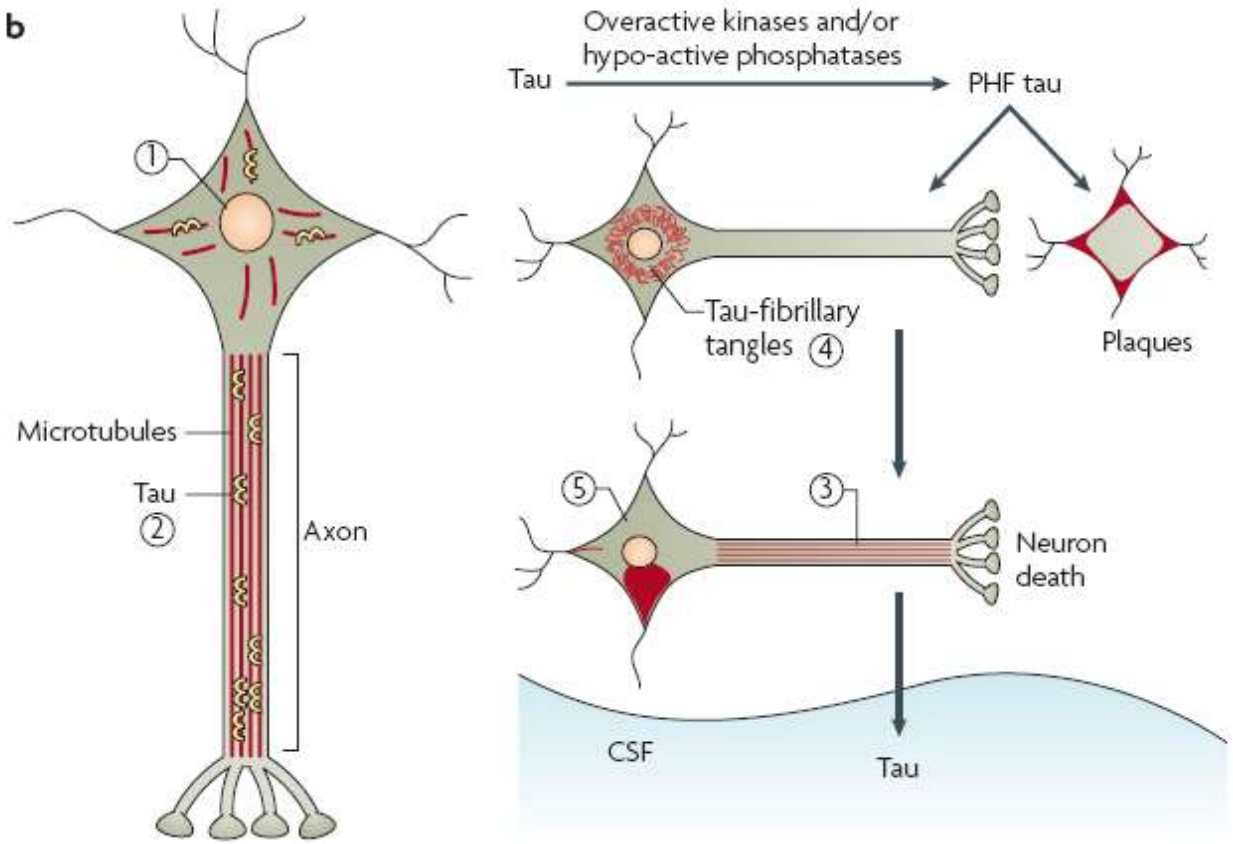
Aβ cascade hypothesis of AD

Hardy J. and Selkoe D. (2002) *Science* **297**:353-6

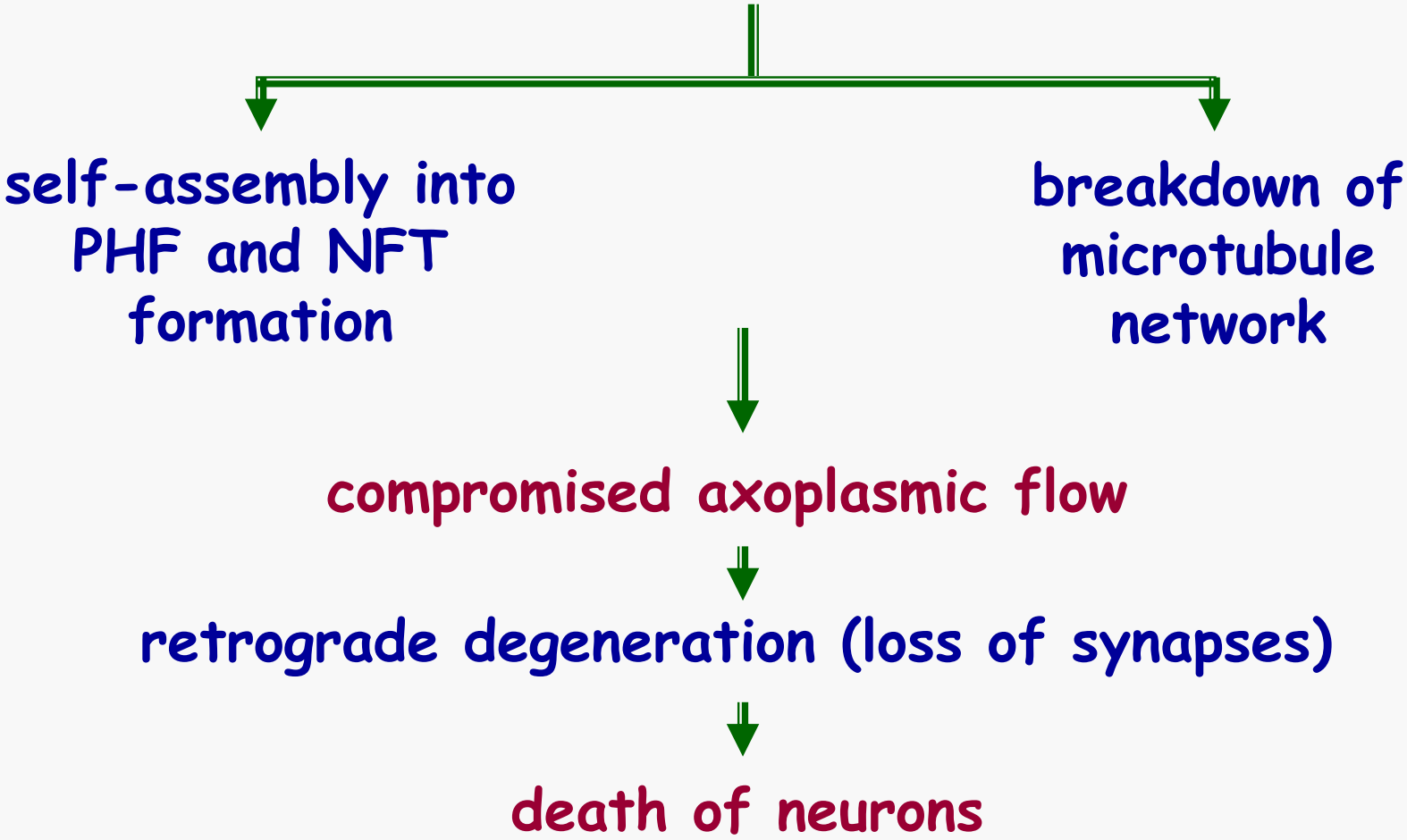


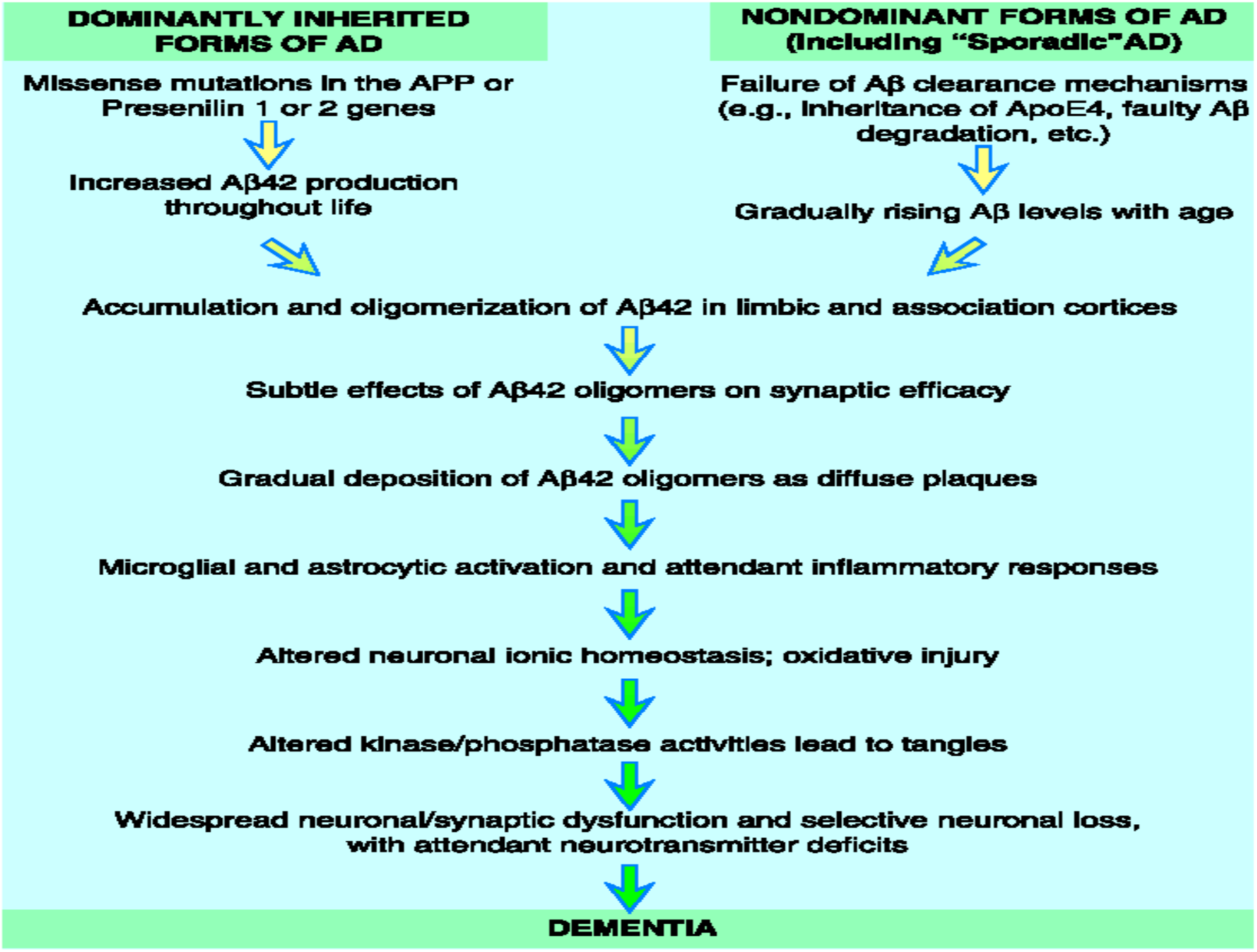
Abeta metabolism



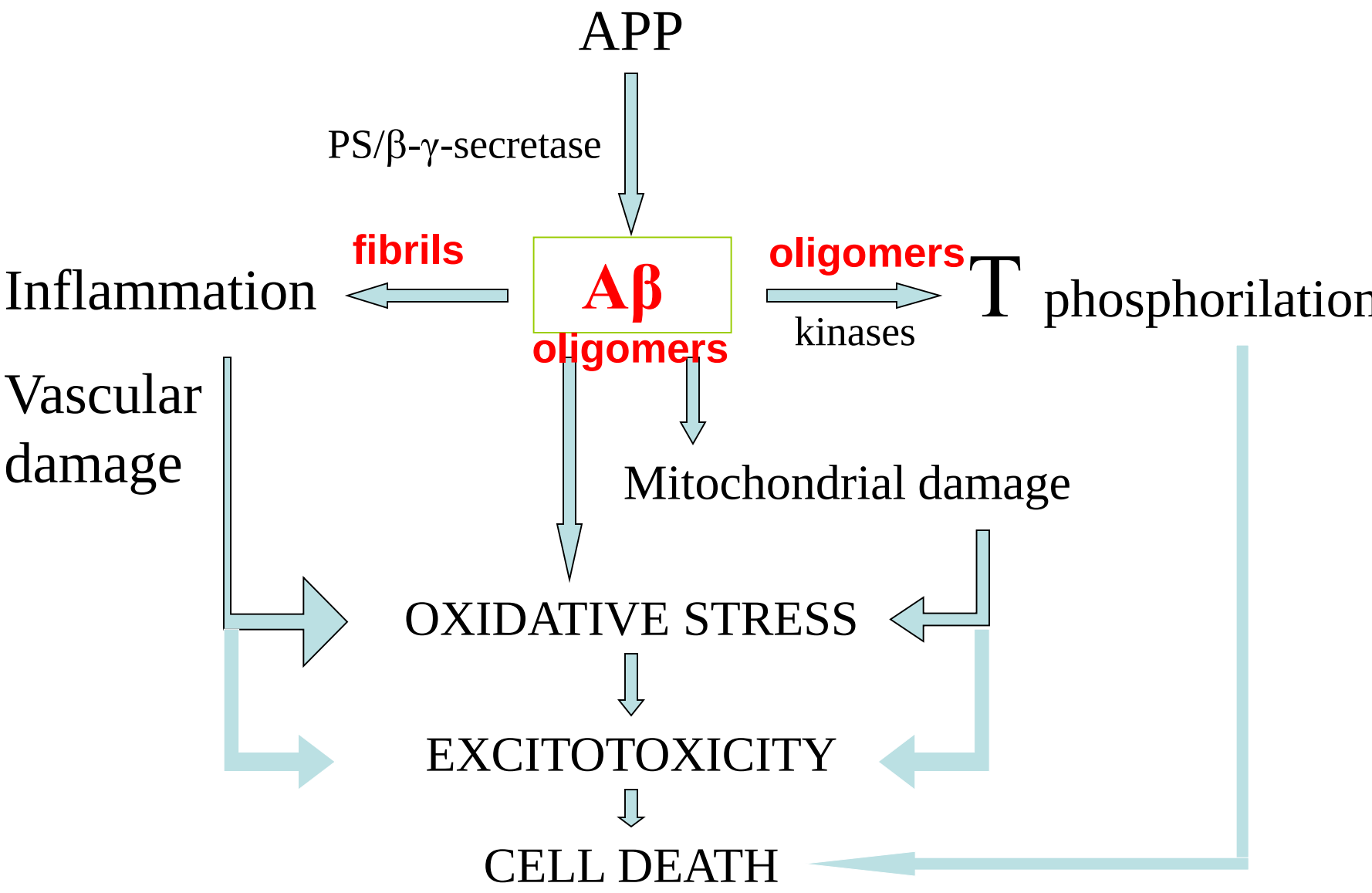

b
1
Microtubules
Tau
2
Axon
Overactive kinases and/or
hypo-active phosphatases
Tau
PHF tau
Tau-fibrillary
tangles 4
Plaques
5
3
Neuron
death
CSF
Tau

tau hyperphosphorylation




DOMINANTLY INHERITED FORMS OF AD
NONDOMINANT FORMS OF AD (Including "Sporadic" AD)
Missense mutations in the APP or Presenilin 1 or 2 genes
Increased Aβ42 production throughout life
Failure of Aβ clearance mechanisms (e.g., Inheritance of ApoE4, faulty Aβ degradation, etc.)
Gradually rising Aβ levels with age
Accumulation and oligomerization of Aβ42 in limbic and association cortices
Subtle effects of Aβ42 oligomers on synaptic efficacy
Gradual deposition of Aβ42 oligomers as diffuse plaques
Microglial and astrocytic activation and attendant inflammatory responses
Altered neuronal ionic homeostasis; oxidative injury
Altered kinase/phosphatase activities lead to tangles
Widespread neuronal/synaptic dysfunction and selective neuronal loss, with attendant neurotransmitter deficits
DEMENTIA

Parallel rather than serial events triggered by Aβ

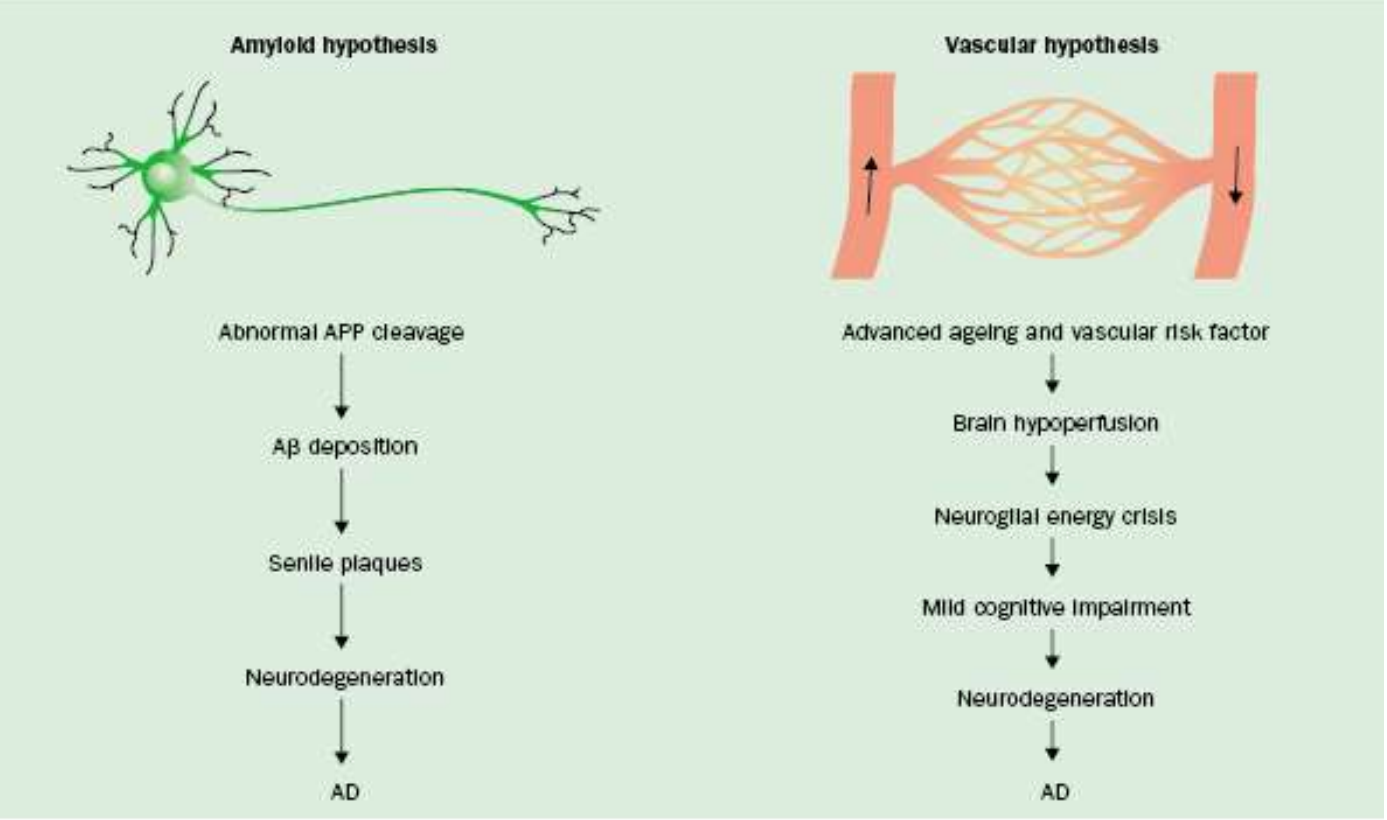


Target: Aβ monomers, oligomers, fibrils, Aβ-related pathways?

Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics

Jack C de la Torre

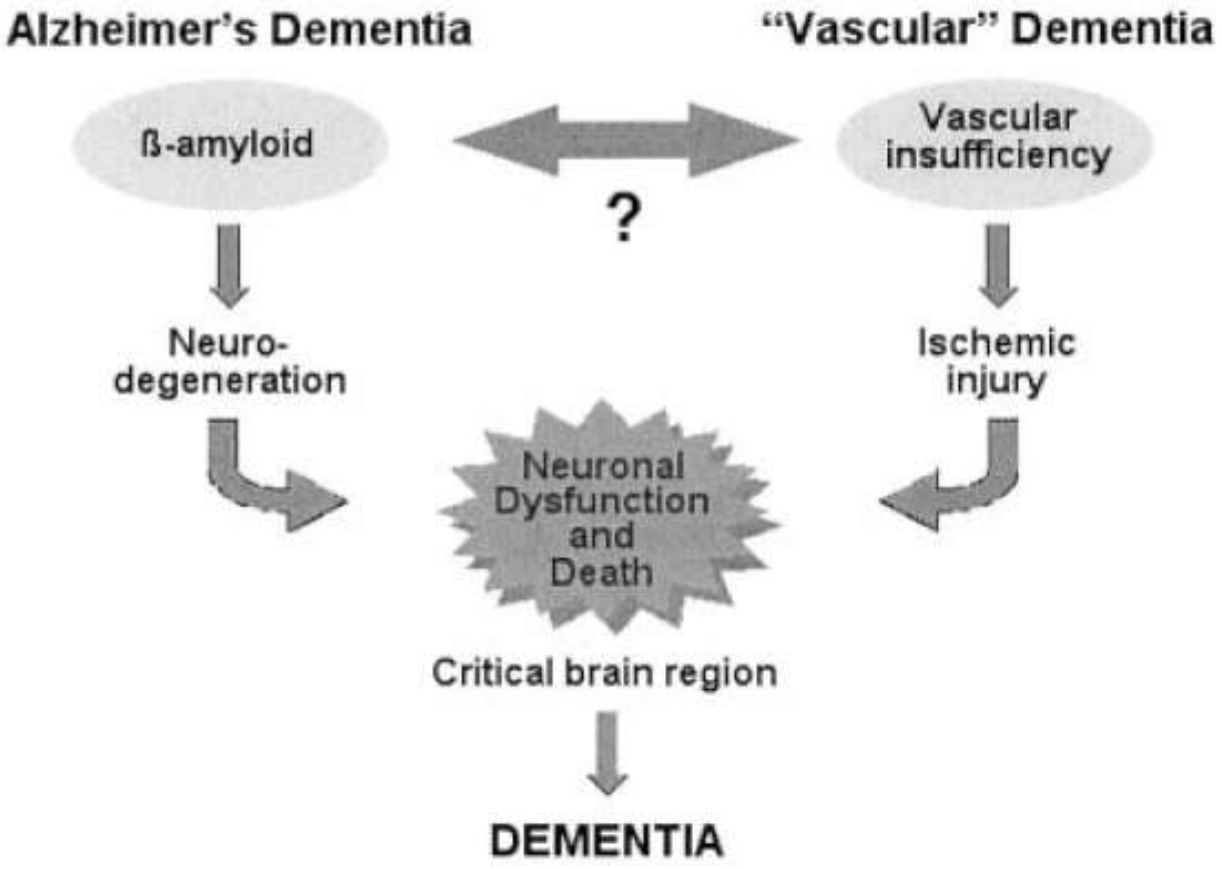
Lancet Neurol 2004; 3: 184–90



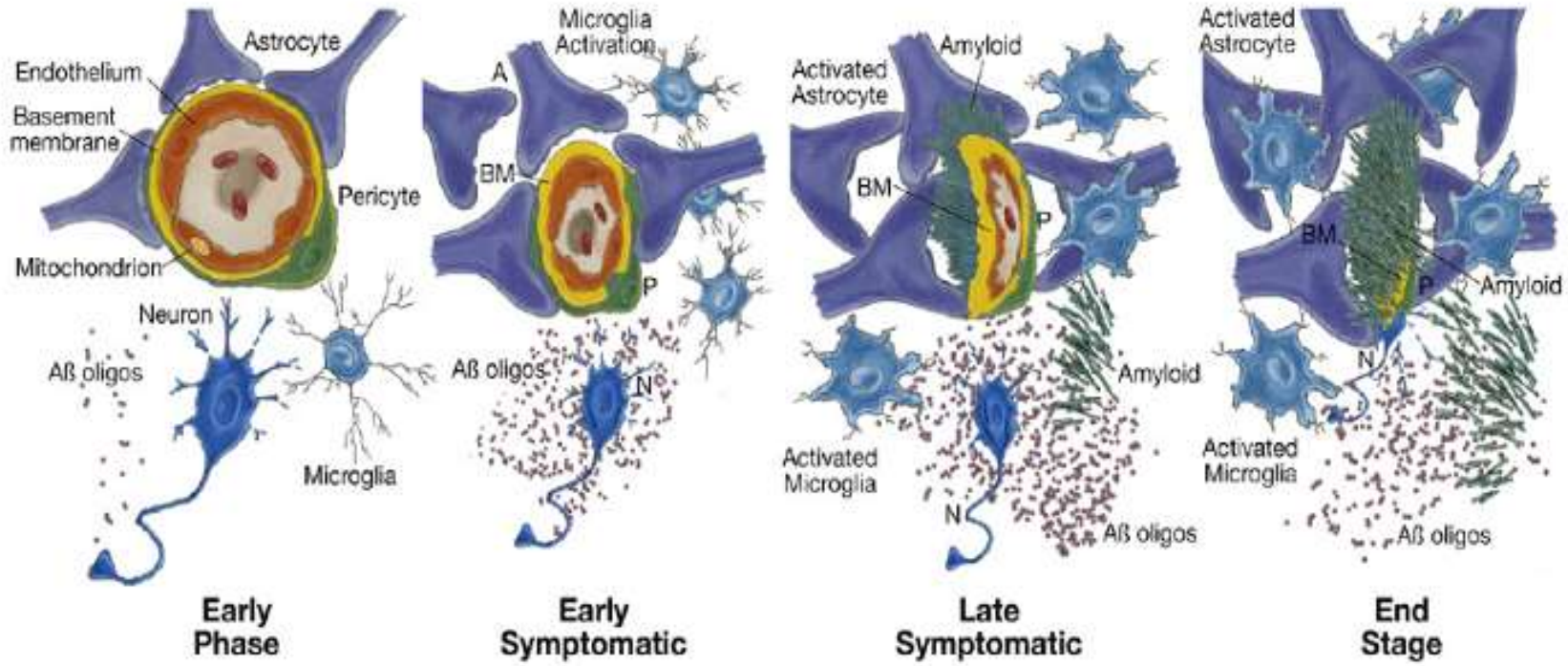
Stroke 2003;34;335-337

Converging Pathogenic Mechanisms in Vascular and Neurodegenerative Dementia

Costantino Iadecola, MD; Philip B. Gorelick, MD, MPH, FACP

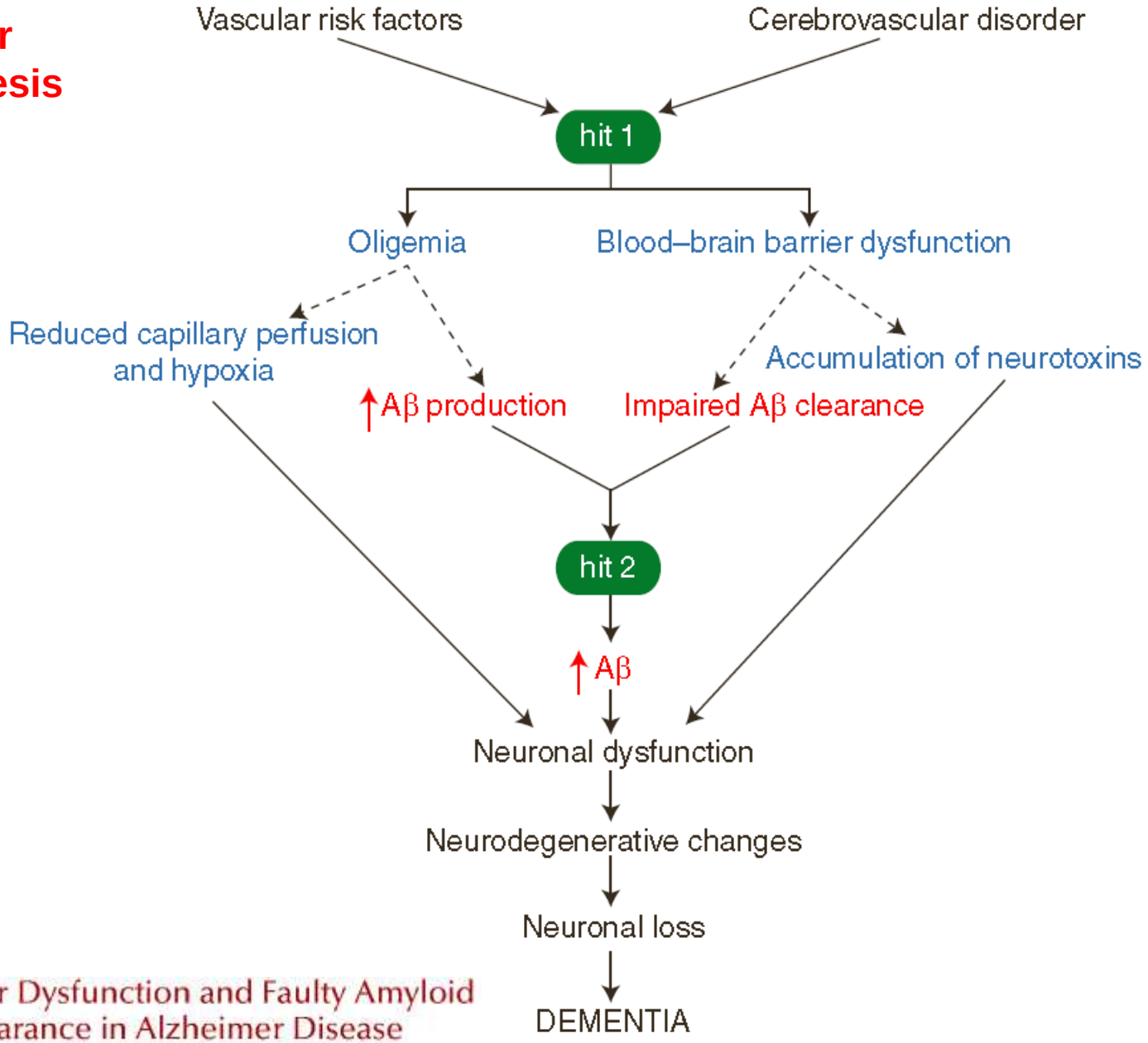


Cerebral Amyloid Angiopathy



Could Abeta deposition both induce and be induced by vascular damage?

Vascular Hypothesis

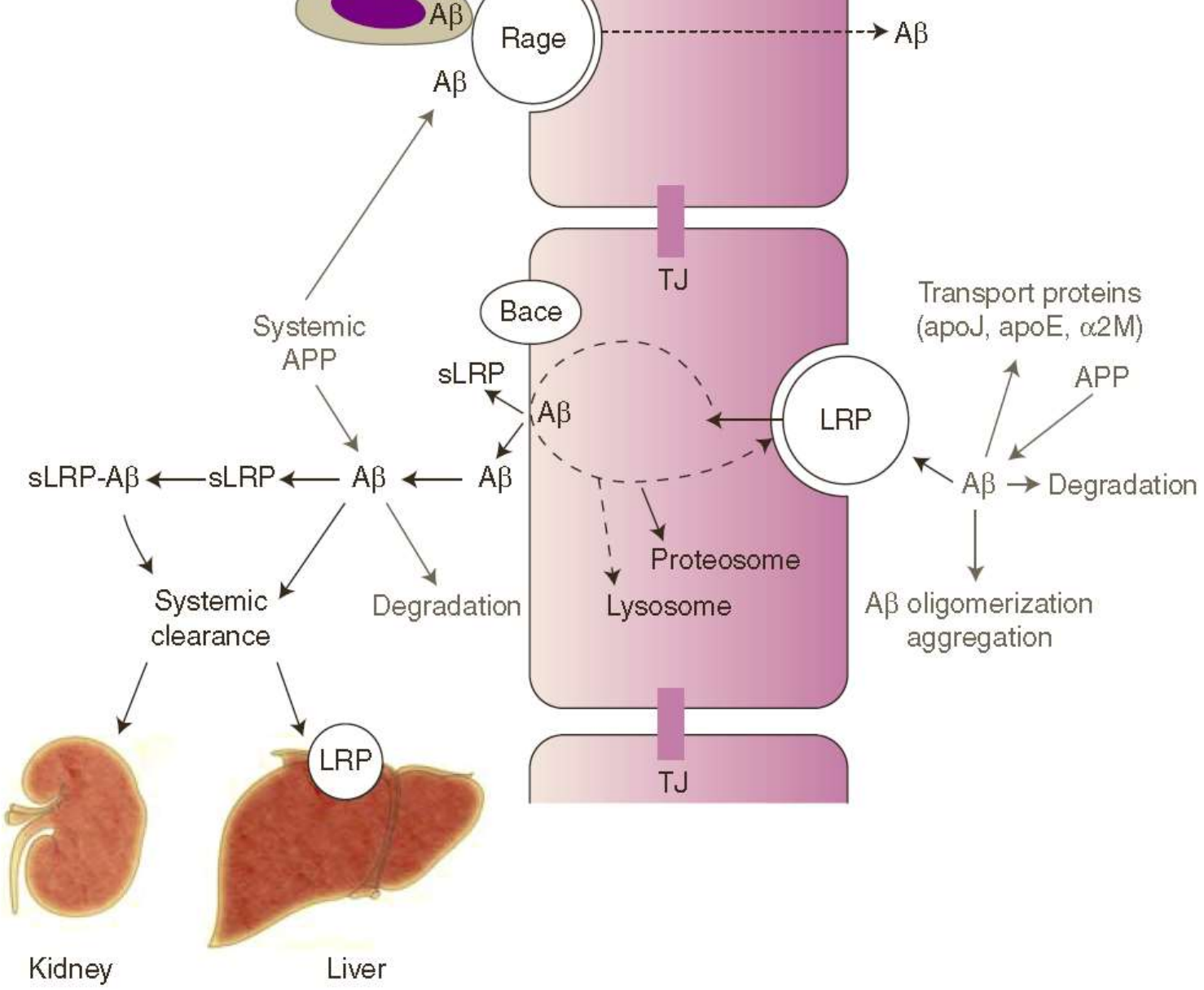


Neurovascular Dysfunction and Faulty Amyloid β-Peptide Clearance in Alzheimer Disease

Abhay P. Sagare, Robert D. Bell, and Berislav V. Zlokovic

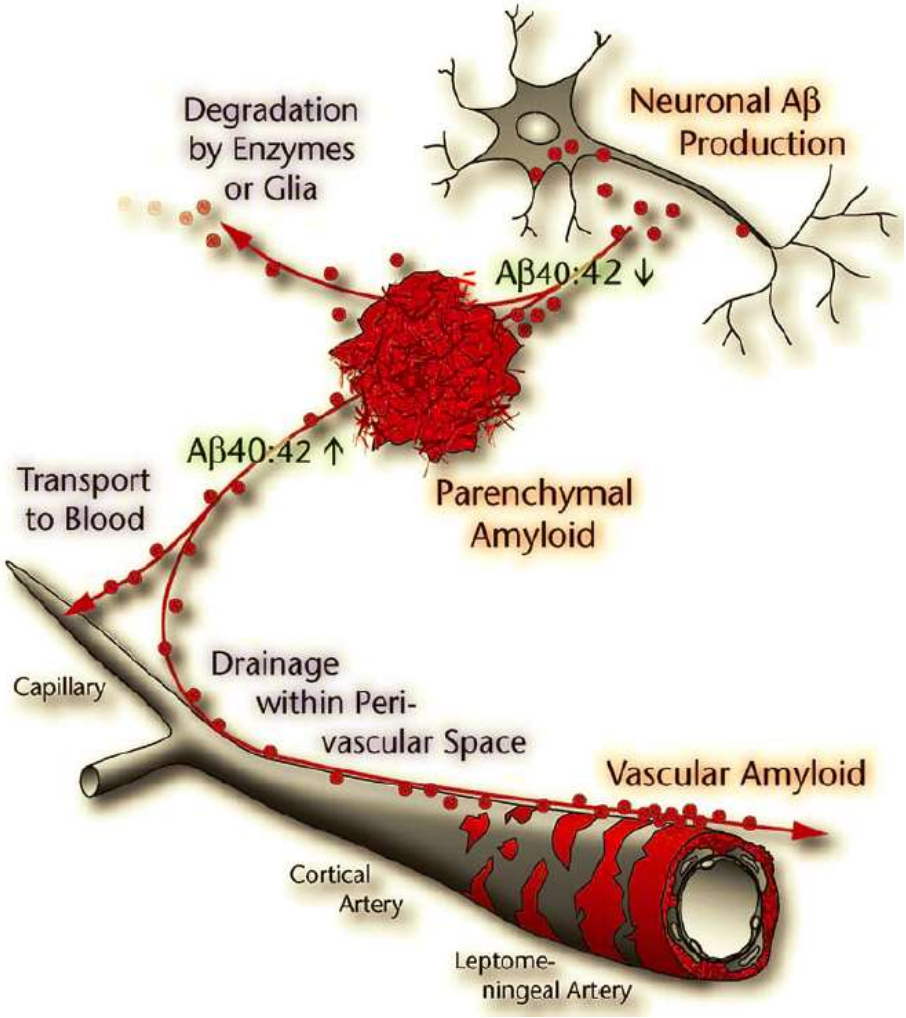
Cold Spring Harb Perspect Med 2012;2

Mechanisms of Abeta clearance through vessel walls



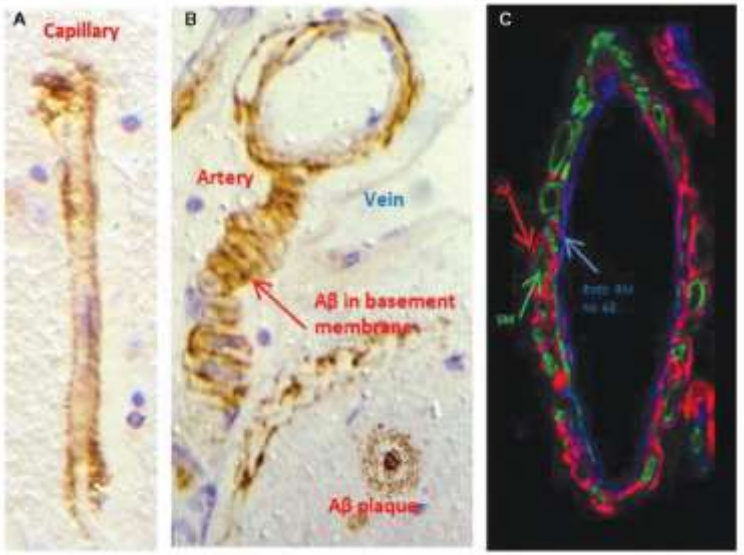
Neurovascular Dysfunction and Faulty Amyloid β-Peptide Clearance in Alzheimer Disease

Abhay P. Sagare, Robert D. Bell, and Berislav V. Zlokovic



Abeta drainage within perivascular space

Failure of Abeta drainage: CAA



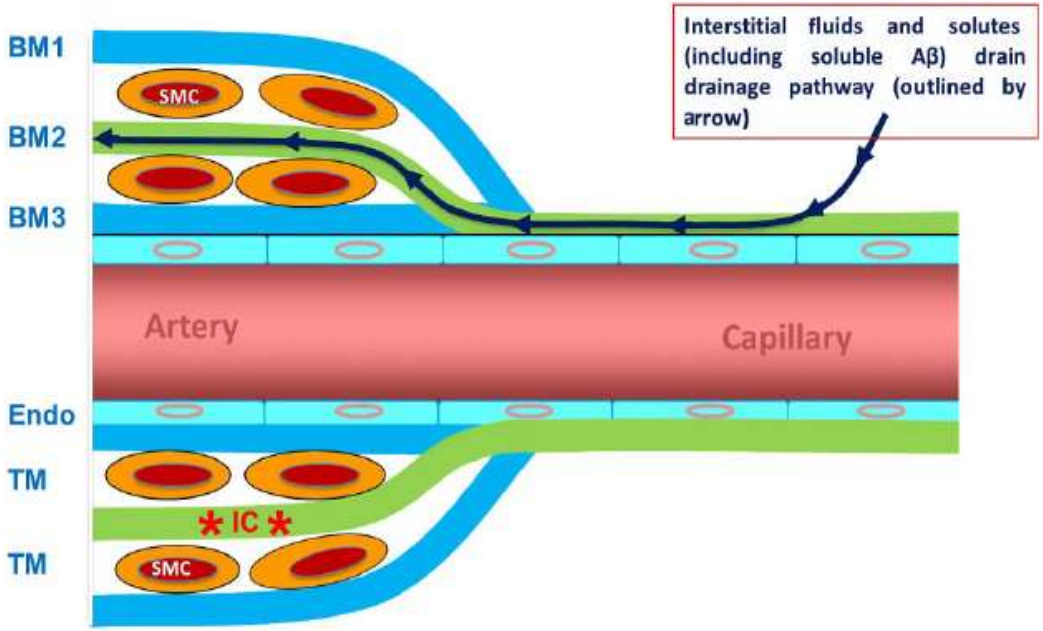
Brain Pathology **25** (2015) 63–78

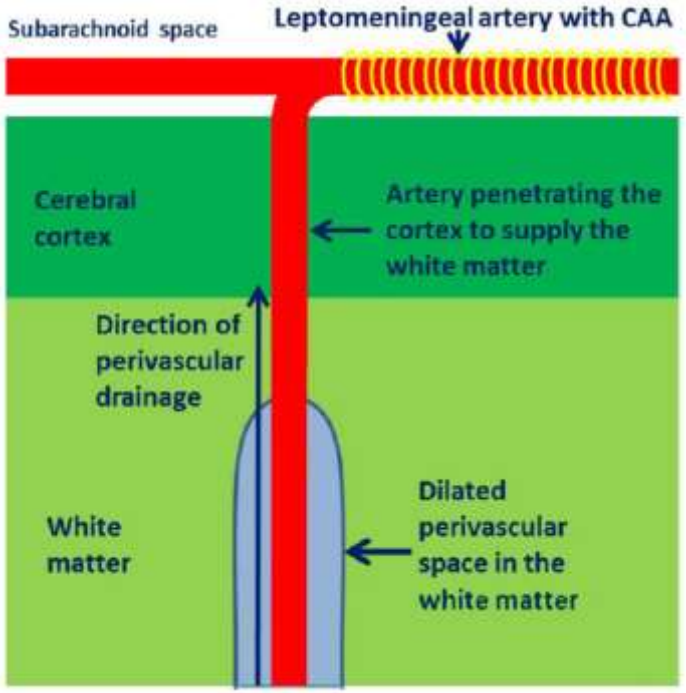
Mechanism of Cerebral β-Amyloid Angiopathy: Murine and Cellular Models

Martin C. Herzig[1,2]; William E. Van Nostrand[3]; Mathias Jucker[1,2]

Brain Pathol 2006;16:40-54.

Age reated impairement of lymphatic drainage lead to white matter changes (T2 and Flair NMR)



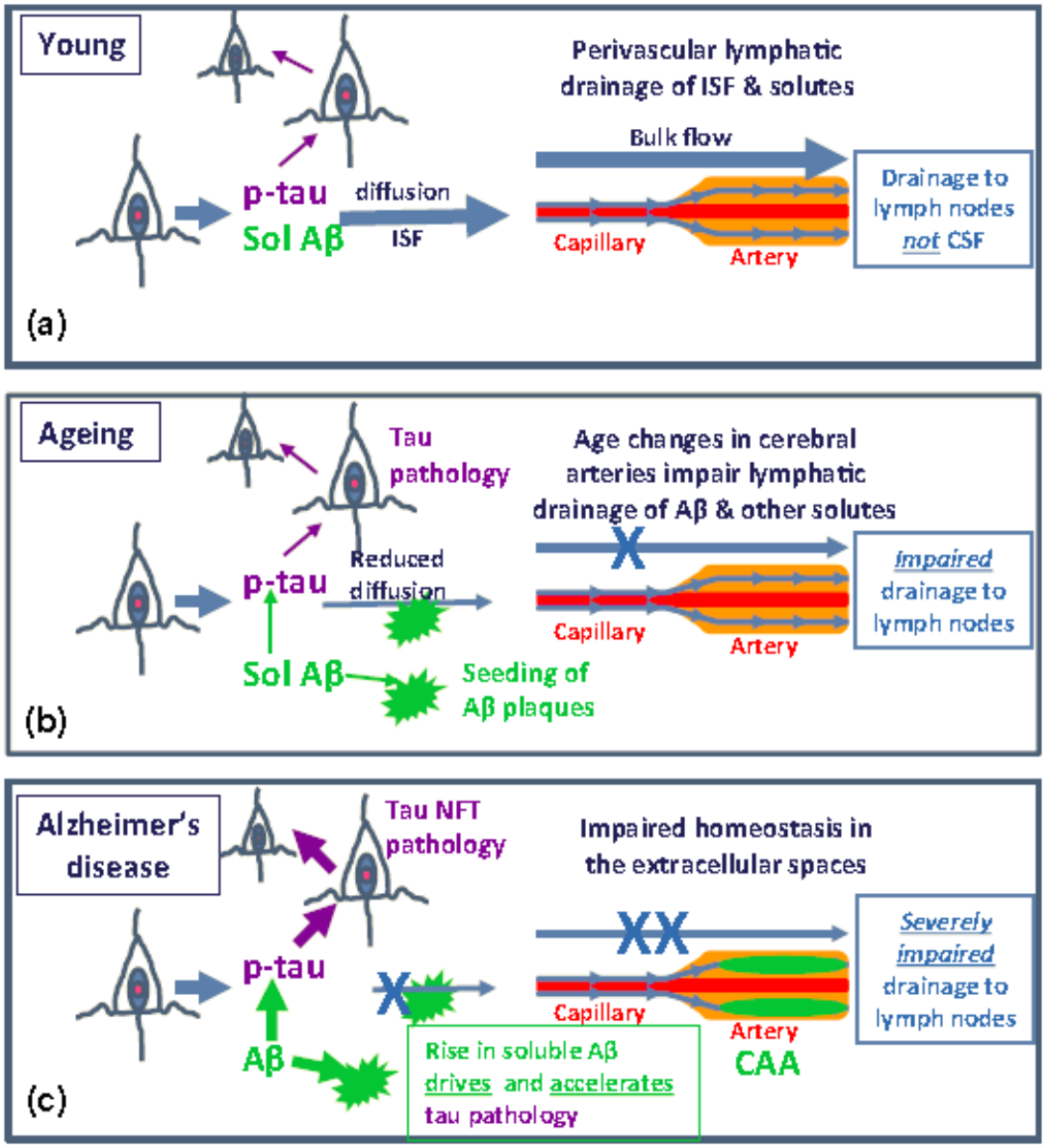


White Matter Changes in Dementia: Role of Impaired Drainage of Interstitial Fluid

Roy O. Weller[1]; Cheryl A. Hawkes[1]; Raj N. Kalaria[2]; David J. Werring[3]; Roxana O. Carare[1]

Brain Pathology **25** (2015) 63–78

Vascular age related changes lead to AD pathology



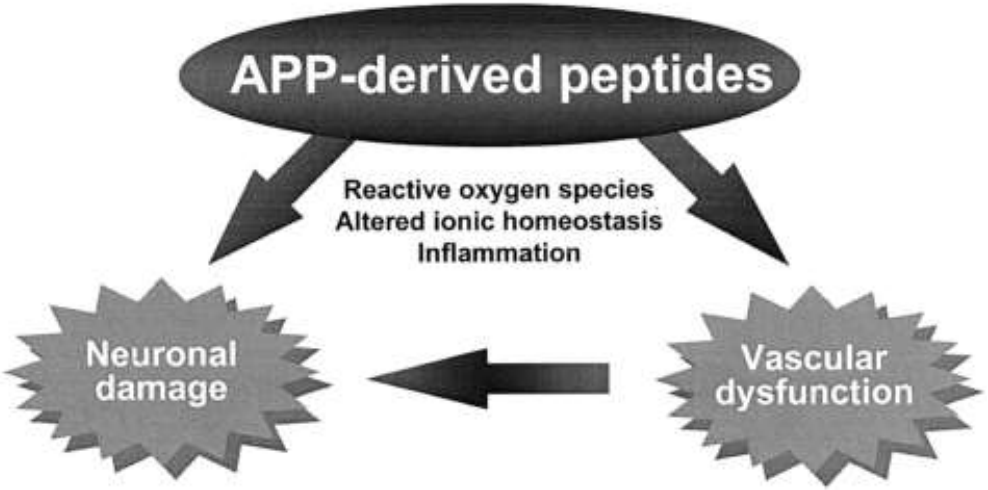
Roy O. Weller[1] · Cheryl A. Hawkes[2] · Roxana O. Carare[1] · John Hardy[3]

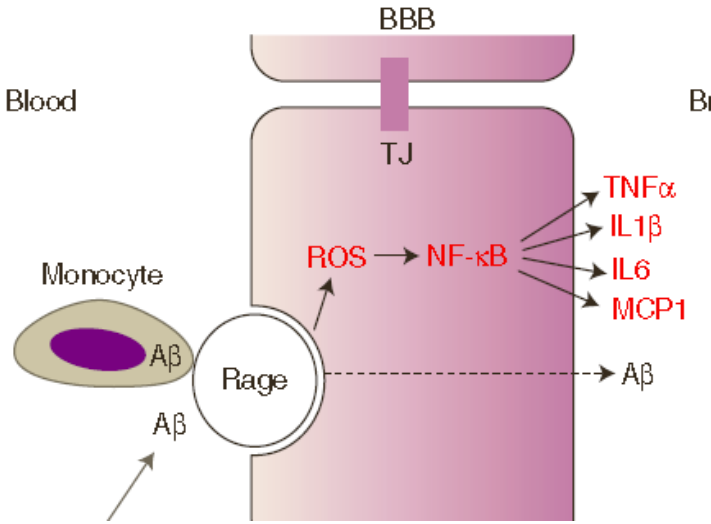
Acta Neuropathol (2015) 129:763–766

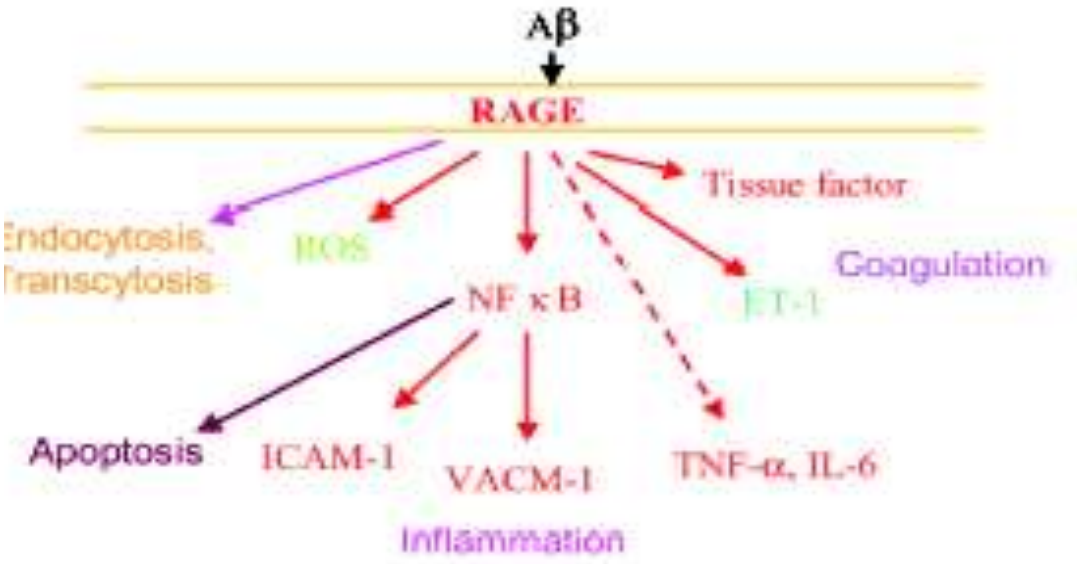
Abeta lead to vascular damage

Cerebrovascular Effects of Amyloid-ß Peptides: Mechanisms and Implications for Alzheimer's Dementia

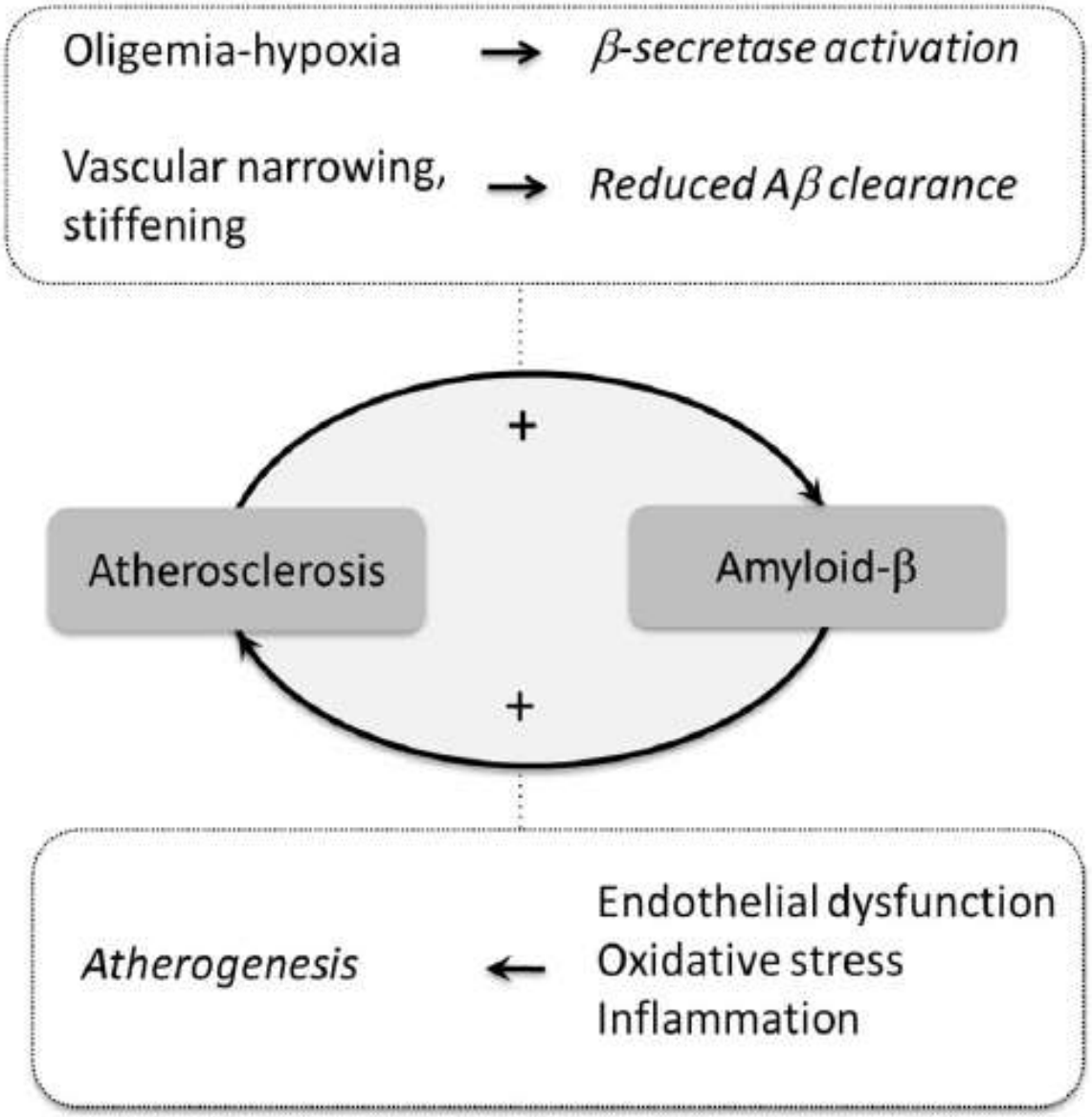
Costantino Iadecola[1,2]





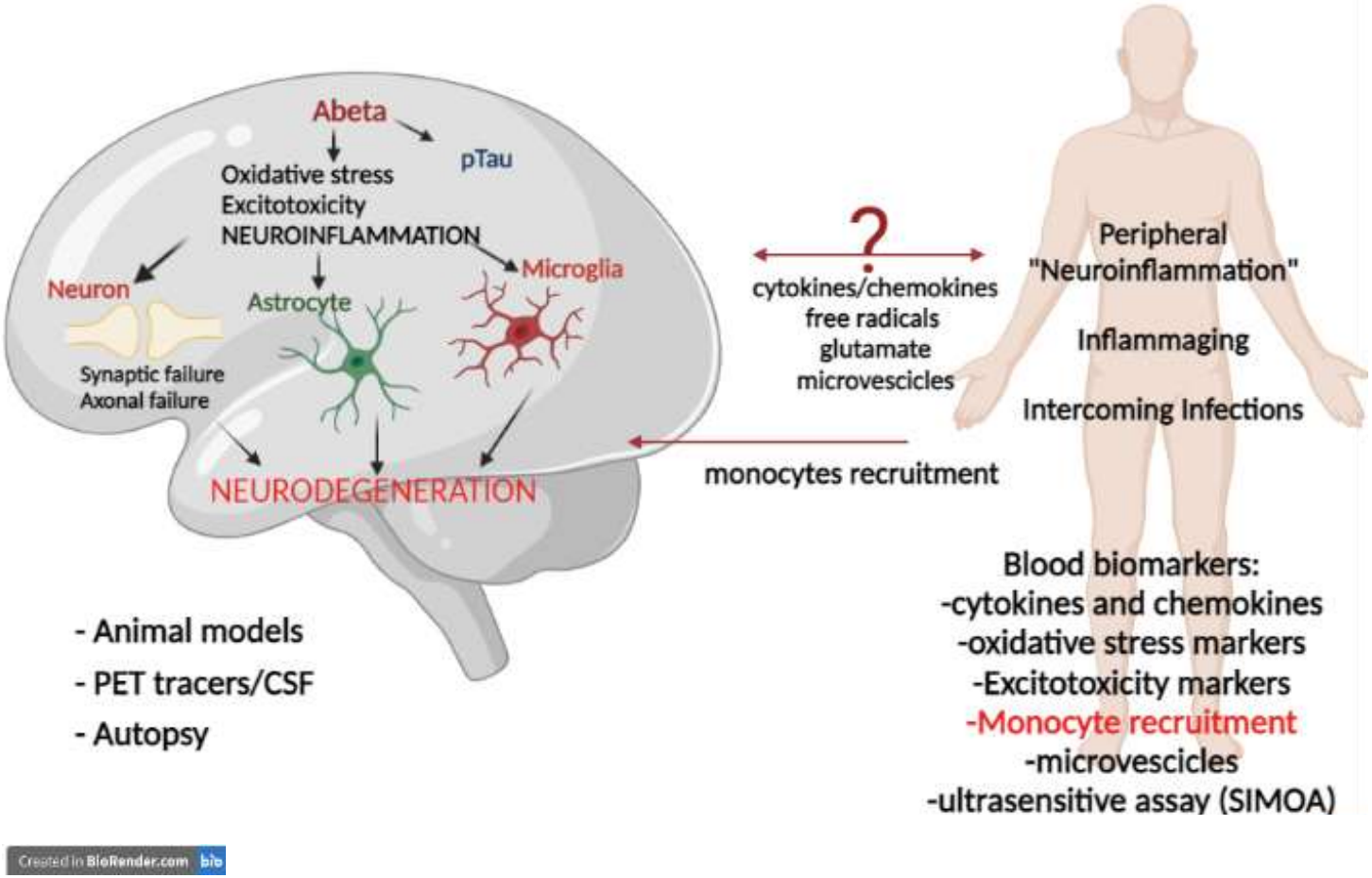


Synergic and bidirectional effect



NEUROINFLAMMATION

CNS-Peripheral immune system: from «Ivory Tower» to integrated system in physiology and in neurodegenerative disorders



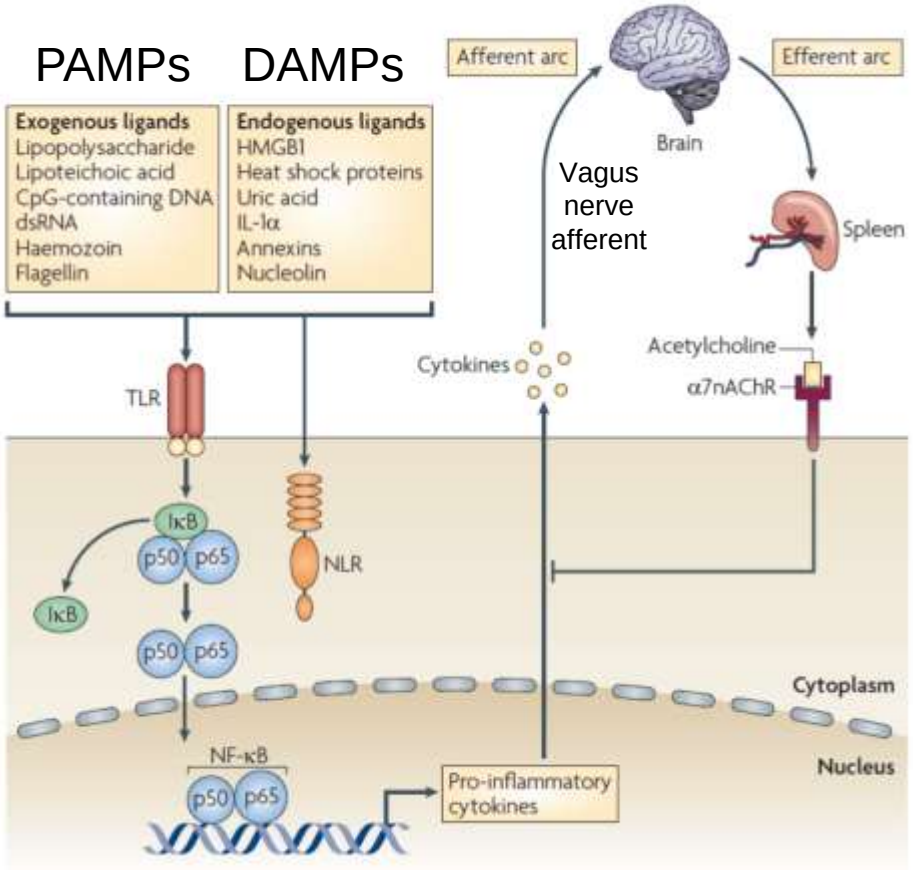
Reflex control of immunity

Kevin J. Tracey

Nature Reviews Immunology **9**, 418–428 (2009)

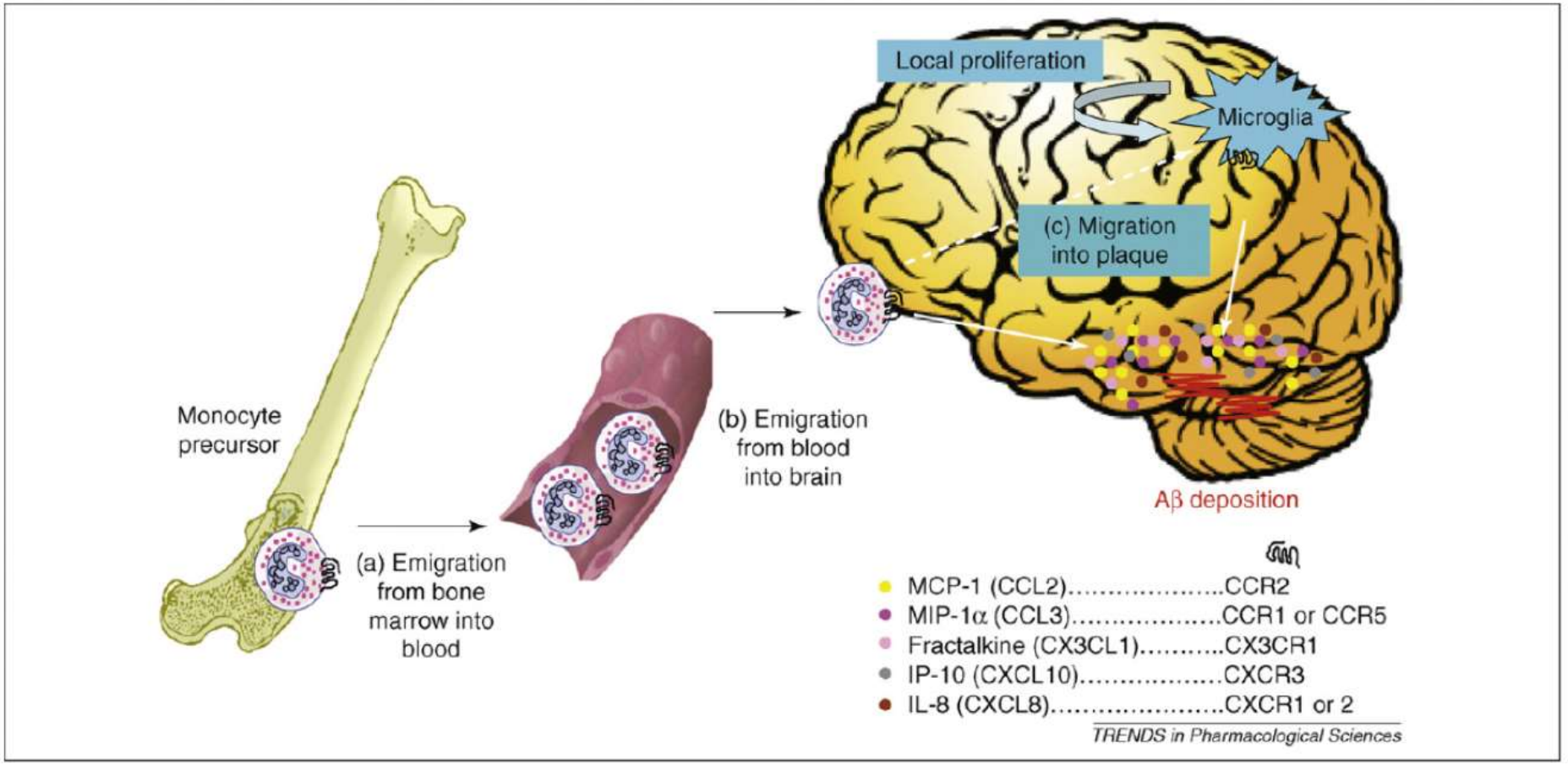
Afferent arc:
peripheral cytokines and vagus nerve

Efferent arc:
vagus nerve



Modified from
NATURE REVIEWS | IMMUNOLOGY 418 | JUNE 2009 | VOLUME 9

Trends in Pharmacological Sciences Vol.29 No.12
2008

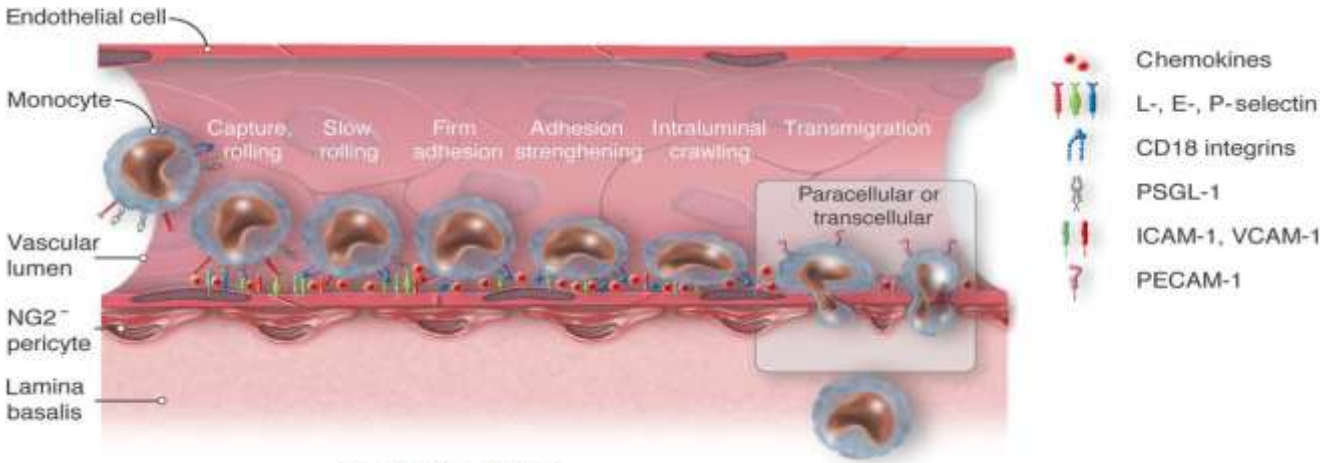


What acts as chemoattractant in brain toward amyloid plaques?

Microglia relased chemochines?

Beta Amyloid?

Both?



T. Gerhardt and K. Ley Cardiovascular Research (2015) **107**, 321–330

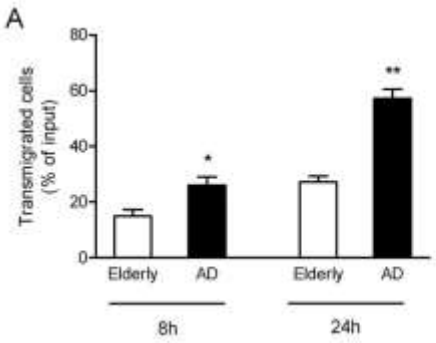
OPEN ACCESS Freely available online

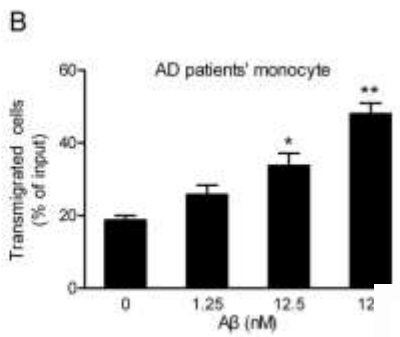
PLOS ONE

CXCL1 Contributes to β-Amyloid-Induced Transendothelial Migration of Monocytes in Alzheimer's Disease

Ke Zhang[1], Li Tian[1], Li Liu[2], Yu Feng[2], Yan-Bin Dong[1], Bo Li[1], De-Shu Shang[1], Wen-Gang Fang[1], Yun-Peng Cao[2], Yu-Hua Chen[1*]

2013





Non physiological **nanomolar** concentrations!

Munawara et al. Immunity & Ageing (2021) 18:29
https://doi.org/10.1186/s12979-021-00236-x

Immunity & Ageing

RESEARCH Open Access

Hyperactivation of monocytes and macrophages in MCI patients contributes to the progression of Alzheimer's disease

Usma Munawara[1], Michael Catanzaro[1,2], Weili Xu[2], Crystal Tan[3], Katsuiku Hirokawa[4], Nabil Bosco[5], David Dumoulin[6], Abdelouahed Khalil[1], Anis Larbi[1,3], Simon Lévesque[7], Charles Ramassamy[8], Annelise E. Barron[9], Stephen Cunnane[10], Pascale B. Beauregard[6], Jean-Pierre Bellenger[11], Serafim Rodrigues[12,13*], Mathieu Desroches[14,15], Jacek M. Witkowski[16], Benoit Laurent[17], Eric H. Frost[7] and Tamas Fulop[1*]

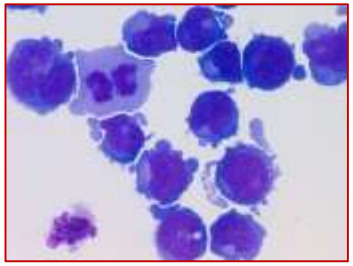
Increased monocytes chemotaxis to MCP-1

Our Aim:

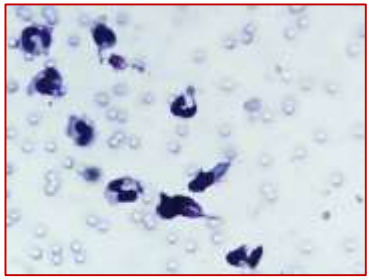
To verify if patho-physiological Abeta 1-42 levels (125 pM) are able to induce monocyte chemotaxis in AD patients. Possible mechanisms?

Models and methods:

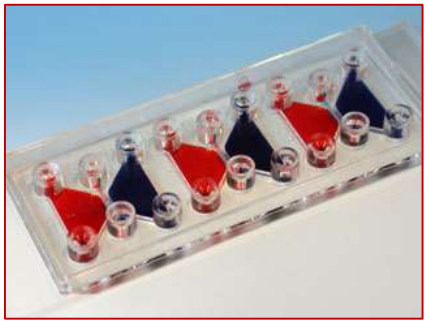
THP-1 cells
(acute monocytic leukemia)



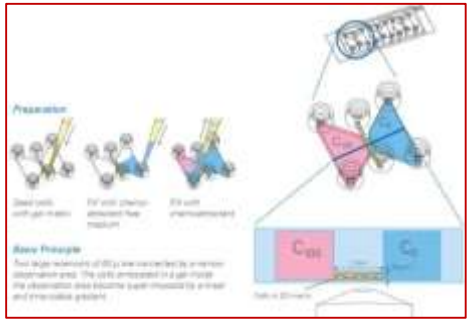
Human Monocytes
(from CTRL and AD)



µ-slide chambers

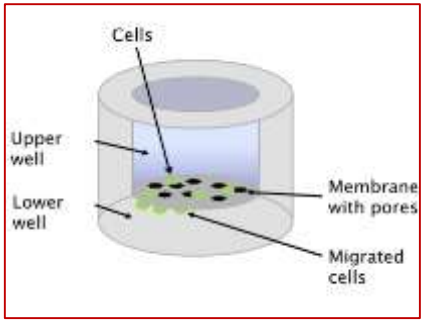


✓ **24 h incubation**
✓ images acquired every 4 minutes with TLM



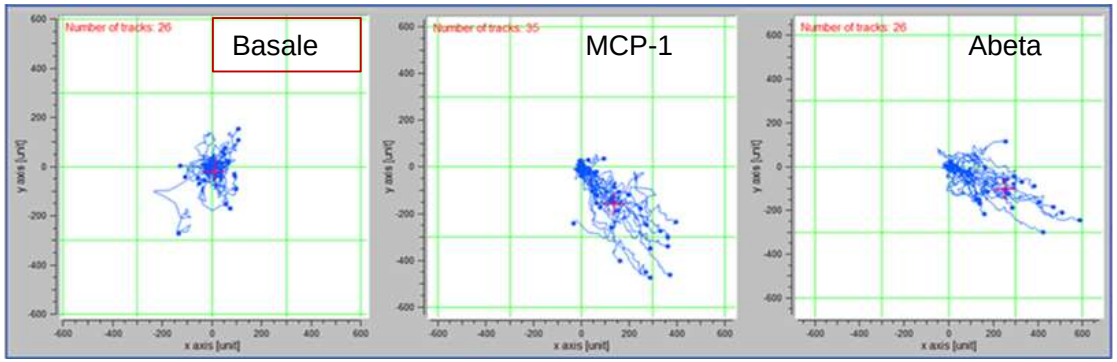
Boyden chambers

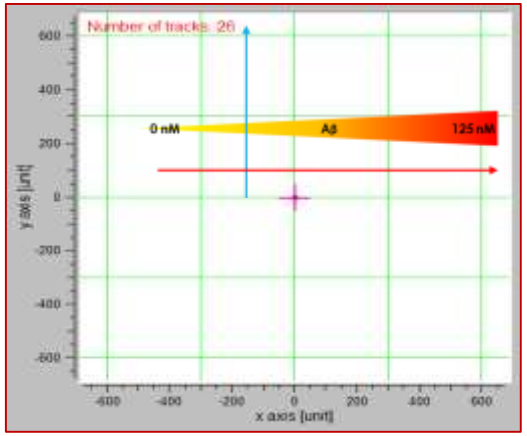
✓ **90 min incubation**
✓ 50˙000 cellule/well
✓ Cells in lower chamber counted

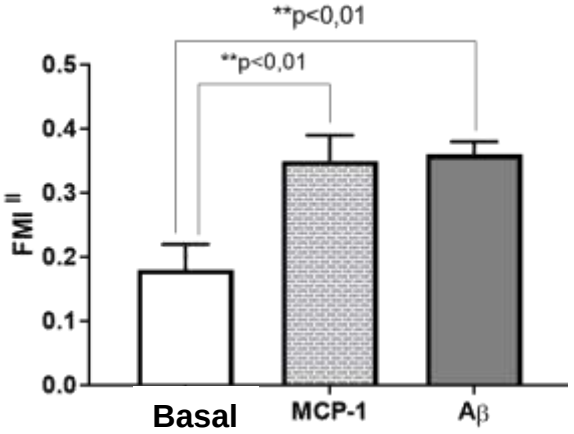


Results: tracking Abeta induced chemotaxis

THP-1

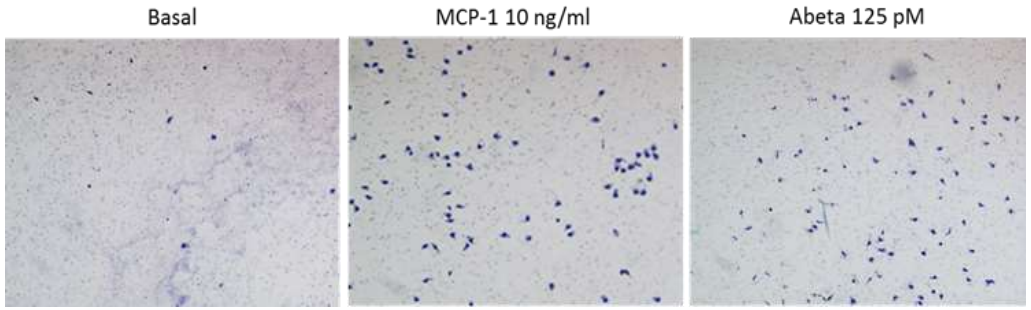


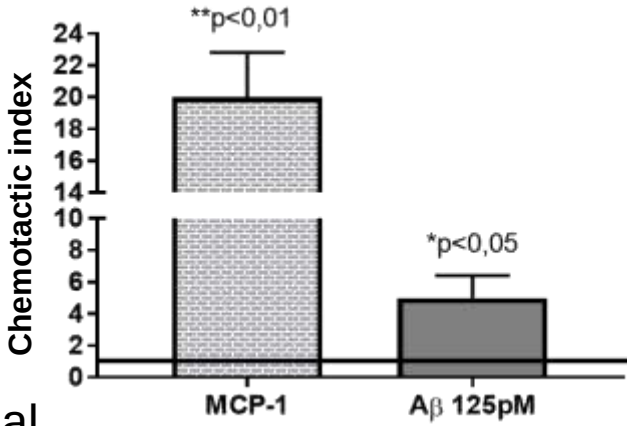




Results: counting cells after Abeta induced chemotaxis

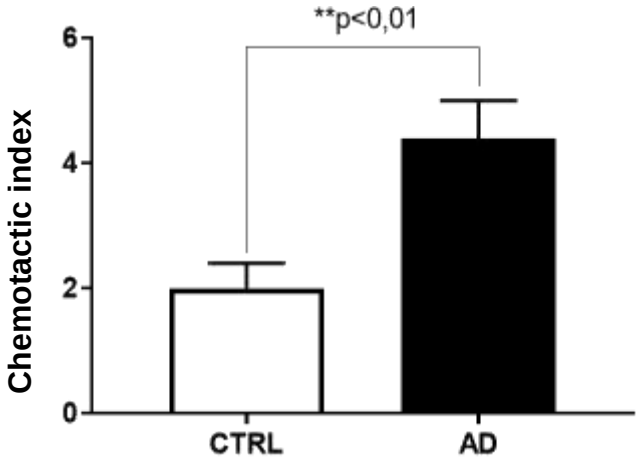
Human monocytes



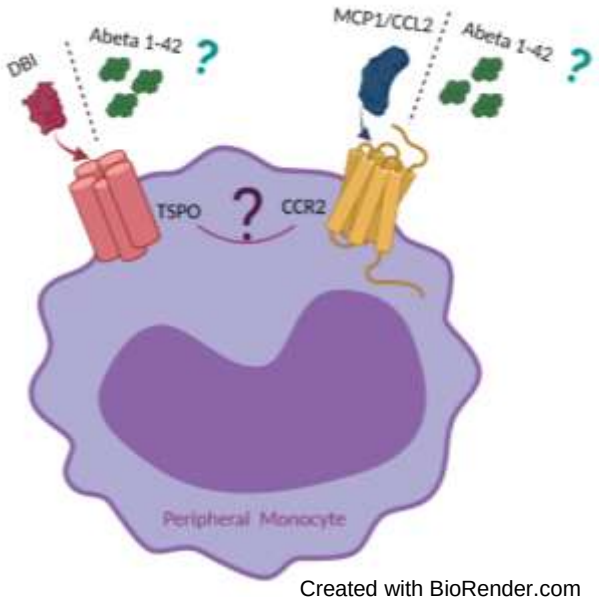


1= Basal

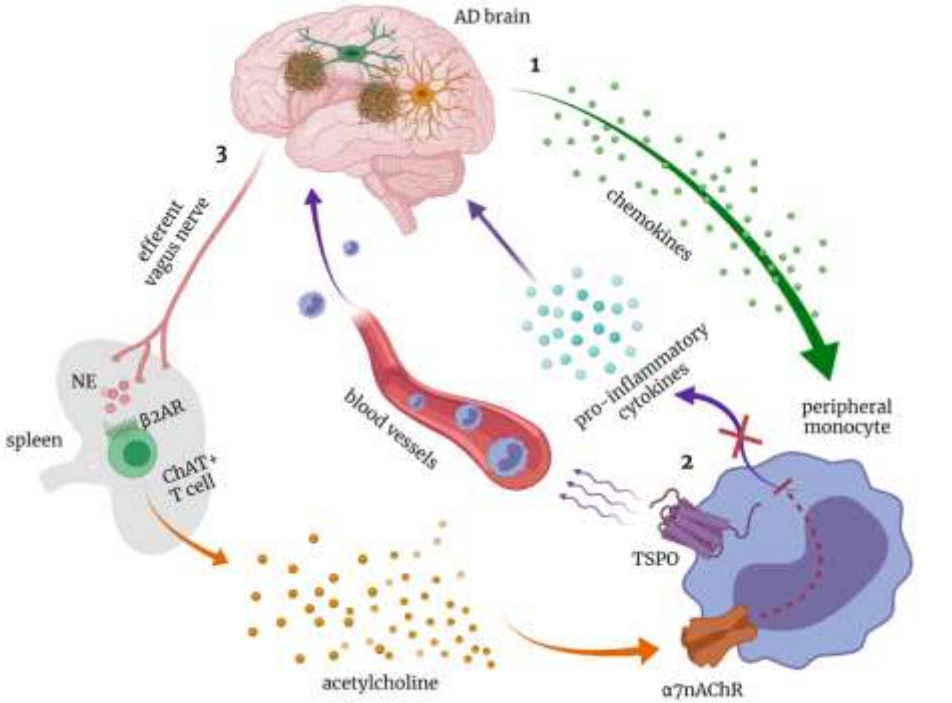
Oligomeric Abeta 1-42 125 pM



Which receptors may be involved in Abeta-induced chemotaxis?



Created with BioRender.com



diagnostics

MDPI

Review

Biomarkers of neuroinflammation in Alzheimer's disease: a central role for periphery?

Federica Angiulli,[1,2,3] Elisa Conti,[1,2] Chiara Paola Zoia,[1,2] Fulvio Da Re,[4] Ildebrando Appollonio,[1,2,4] Carlo Ferrarese,[1,2,4] Lucio Tremolizzo[1,2,4]

Submitted

Mechanisms involved in Abeta induced chemotaxis: Possible role of PBR/TSPO receptor?

Neuropharmacology Vol. 29, No. 4, pp. 375–378, 1990
Printed in Great Britain.

CHARACTERIZATION OF PERIPHERAL BENZODIAZEPINE RECEPTORS IN HUMAN BLOOD MONONUCLEAR CELLS

C. FERRARESE,[1,*] I. APPOLLONIO,[1] M. FRIGO,[1] M. PEREGO,[1] C. PIERPAOLI,[1] M. TRABUCCHI[2] and L. FRATTOLA[1]

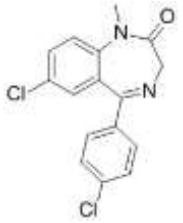
Translocator protein (18 kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function

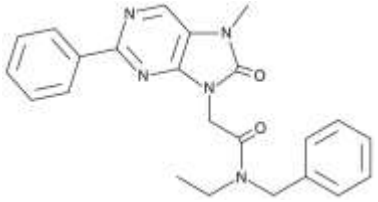
Vassilios Papadopoulos[1], Mario Baraldi[2], Tomás R. Guilarte[3], Thomas B. Knudsen[4], Jean-Jacques Lacapère[5], Peter Lindemann[6], Michael D. Norenberg[7], David Nutt[8], Abraham Weizman[9], Ming-Rong Zhang[10] and Moshe Gavish[11]

Exogenous PBR (TSPO) ligands

Agonists

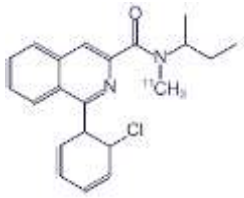
- Ro5-4864
- Emapunil (XBD-173)





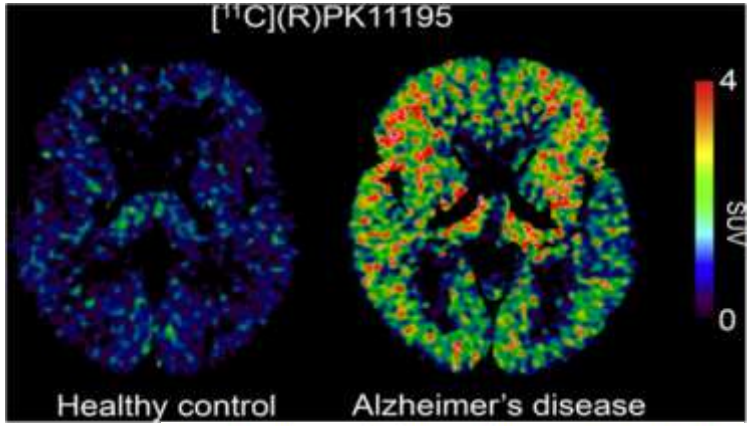
Antagonist

- PK11195



Microglial activation is revealed by **PK11195 binding to TSPO receptor**

First studies on microglial activation in neurodegenerative diseases



Zimmer *et al. Journal of Neuroinflammation* 2014, **11**:120

Brain (2000), 123, 2321

The peripheral benzodiazepine binding site in the brain in multiple sclerosis

Quantitative *in vivo* imaging of microglia as a measure of disease activity

R. B. Banati,[1,10] J. Newcombe,[4] R. N. Gunn,[1] A. Cagnin,[1] F. Turkheimer,[1] F. Heppner,[5,11] G. Price,[7]

In-vivo measurement of activated microglia in dementia

THE LANCET • Vol 358 • August 11, 2001

Annachiara Cagnin, David J Brooks, Angus M Kennedy, Roger N Gunn, R Myers, Federico E Turkheimer, Terry Jones, Richard B Banati

Clinical Trial > Neurology. 2006 Jun 13;66(11):1638-43.

doi: 10.1212/01.wnl.0000222734.56412.17.

Microglial activation correlates with severity in Huntington disease: a clinical and PET study

N Pavese [1], A Gerhard, Y F Tai, A K Ho, F Turkheimer, R A Barker, D J Brooks, P Piccini

ORIGINAL ARTICLES Ann Neurol 2005;57:168–175

Microglial Activation and Dopamine Terminal Loss in Early Parkinson's Disease

Yasuomi Ouchi, MD, PhD,[1] Etsuji Yoshikawa, BA,[2] Yoshimoto Sekine, MD, PhD,[1,2] Masami Futatsubashi, BA,[2] Toshihiko Kanno, RT,[1] Tomomi Ogusu, MA,[2] Tatsuo Torizuka, MD, PhD[1]

Evidence of widespread cerebral microglial activation in amyotrophic lateral sclerosis: an [11C](R)-PK11195 positron emission tomography study

Neurobiology of Disease 15 (2004) 601–609

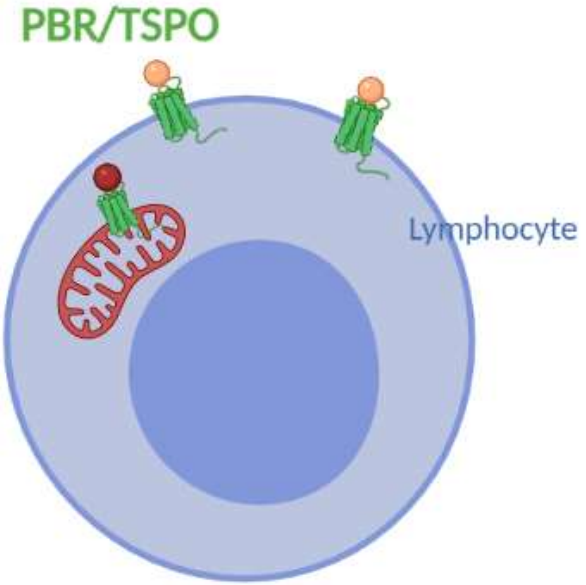
M.R. Turner,[a,b,*] A. Cagnin,[c] F.E. Turkheimer,[b,d] C.C.J. Miller,[a] C.E. Shaw,[a] D.J. Brooks,[b,e] P.N. Leigh,[a] and R.B. Banati[b,d]

Life Sciences
Volume 52, Issue 15, 1993, Pages 1265-1277

Topology of two DBI receptors in human lymphocytes

Alla Berkovich, Carlo Ferrarese, Guido Cavaletti, Hannu Alho, Claudia Marzorati, Graziella Bianchi, Alessandro Guidotti, Erminio Costa

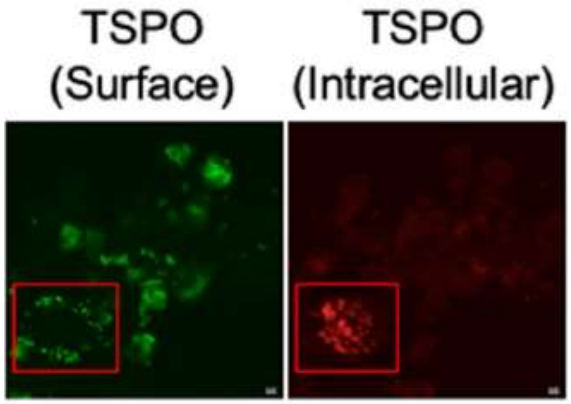
PBR/TSPO is present on mitochondrial and plasma membrane



Surface translocator protein 18 kDa (TSPO) localization on immune cells upon stimulation with LPS and in ART-treated HIV+ subjects

J Leukoc Biol. 2021;110:123–140.

Lance K. Blevins[1] | Robert B. Crawford[1] | Diana J. Azzam[2] | Tomás R. Guilarte[2] | Norbert E. Kaminski[1]

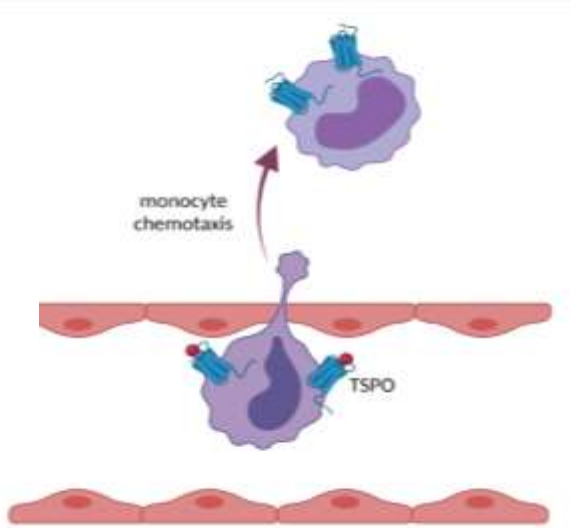


Life Sciences, Vol. 53, pp. 653-658 1993
Printed in the USA

Pergamon Press

BENZODIAZEPINE INDUCED CHEMOTAXIS OF HUMAN MONOCYTES: A TOOL FOR THE STUDY OF BENZODIAZEPINE RECEPTORS

Paola Sacerdote, Luisa D.Locatelli,
Alberto E.Panerai



Acta Psychiatr Scand. 1990 Aug;82(2):169-73.

Decreased density of benzodiazepine receptors in lymphocytes of anxious patients: reversal after chronic diazepam treatment.

Ferrarese C, Appollonio I, Frigo M, Perego M, Piolti R, Trabucchi M, Frattola L.

PERGAMON

PNEC

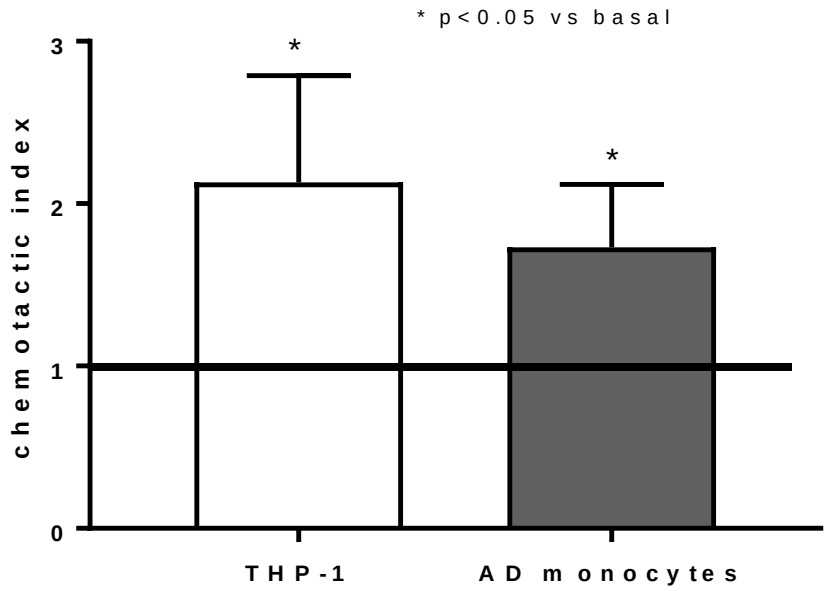
Psychoneuroendocrinology 24 (1999) 243–249

Benzodiazepine-induced chemotaxis is impaired in monocytes from patients with generalized anxiety disorder

P. Sacerdote [a,*], A.E. Panerai [a], L. Frattola [b], C. Ferrarese [b]

Results: TSPO pharmacological modulation

TSPO Agonist: **Ro5-4864 (10 µM) increases basal monocyte chemotaxis**

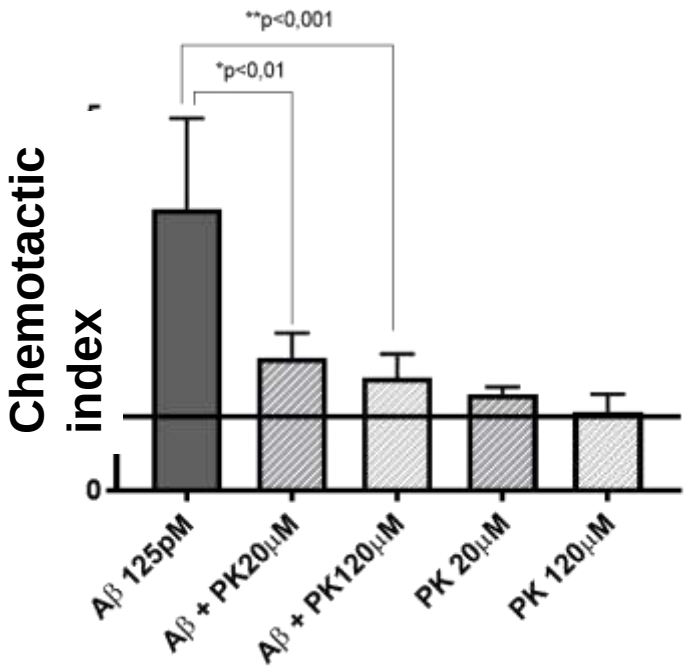


1= Basal

Results: TSPO pharmacological modulation

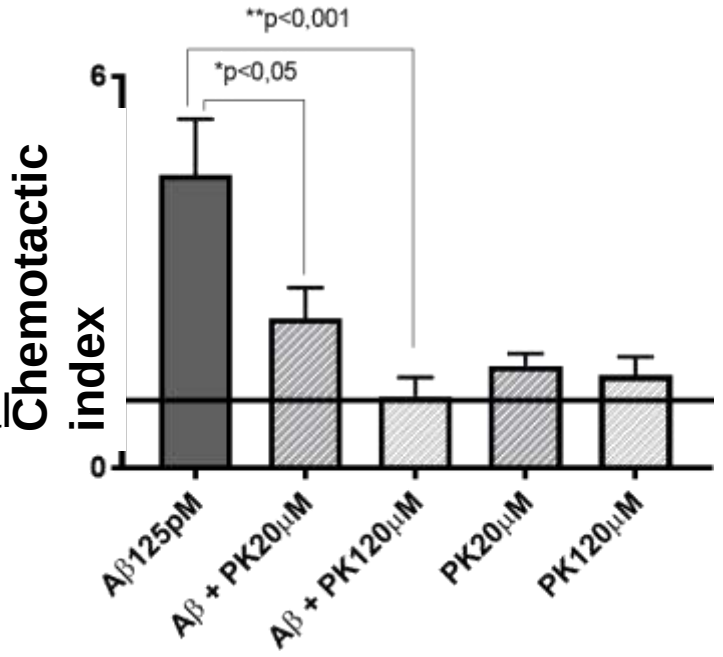
TSPO Antagonist: **PK-11195 blocks Abeta induced chemotaxis**

THP-1

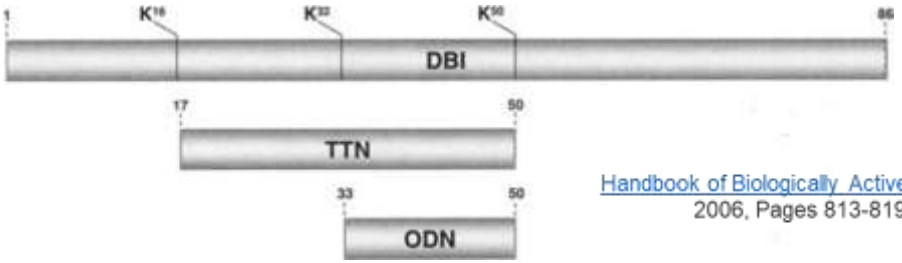


AD Monocytes

1= Basal



Endogenous PBR/TSPO ligands: DBI (Diazepam Binding Inhibitor)



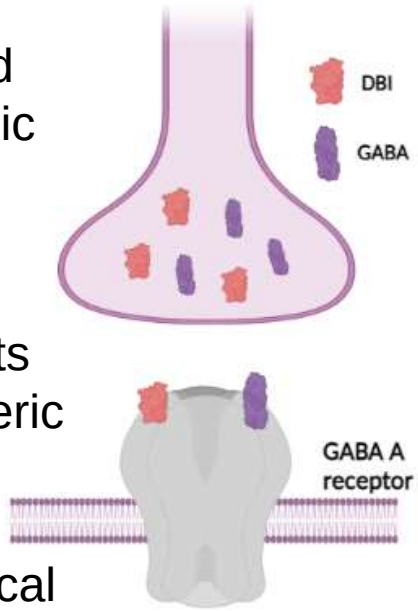
Handbook of Biologically Active Peptides
2006, Pages 813-819

PROCESSING OF DBI (biologically active peptides):

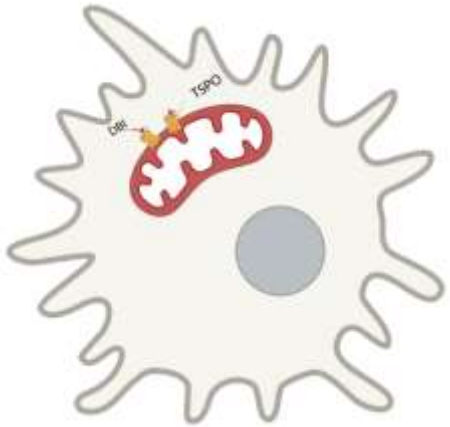
- triakontatetraneuropeptide TTN (DBI17–50)
- octadecaneuropeptide ODN (DBI33–50)

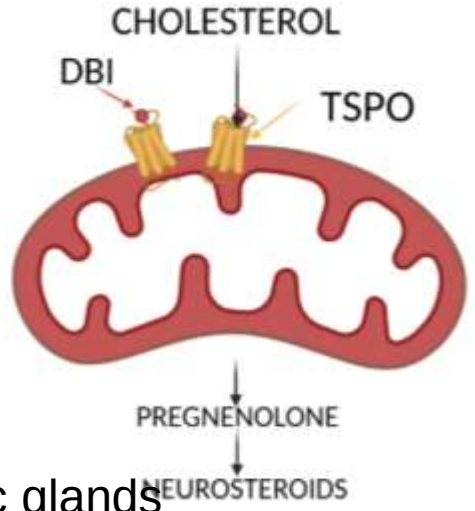
1. DBI is released from GABAergic neurons

Binds Central Benzodiaz. Receptors and acts as negative allosteric modulator
→ansiogenic and epileptogenic clinical effect



2. DBI binds PBR/TSPO in mitochondria of glial cells/steroidogenic glands and lymphomonocytes





Glial cells, steroidogenic glands

Is there a role for endogenous ligands?

NEUROLOGY 1990;40:632-635

Cerebrospinal fluid levels of diazepam-binding inhibitor in neurodegenerative disorders with dementia

C. Ferrarese, MD, PhD; L. Appollonio, MD; M. Frigo, MD; S. Meregalli, MD; R. Piolti, MD; F. Tamma, MD; and L. Frattola, MD

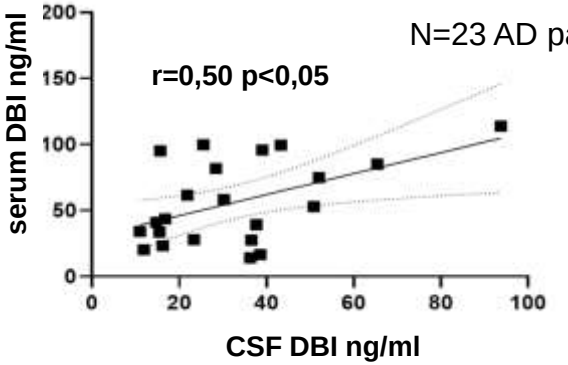
DBI levels in CSF

Patients		DBI-LI Means ± SD	Range
Controls (>50 yrs)	(n = 14)	1.0 ± 0.24	0.8-1.4
Parkinson's disease	(n = 28)	1.4 ± 0.53	0.6-3.0
Treated	(n = 22)	1.5 ± 0.60	0.6-3.0
Untreated	(n = 6)	1.2 ± 0.30	0.8-2.1
Demented	(n = 14)	2.1 ± 0.60†	1.0-3.0
Not demented	(n = 14)	0.85 ± 0.28	0.6-1.4
Controls (<50 yrs)	(n = 10)	0.95 ± 0.36	0.6-1.2
Huntington's chorea	(n = 7)	0.67 ± 0.19*	0.4-0.8
Controls (>50 yrs)	(n = 10)	1.0 ± 0.24	0.8-1.4
Alzheimer's disease	(n = 10)	2.1 ± 0.60‡	1.4-3.1

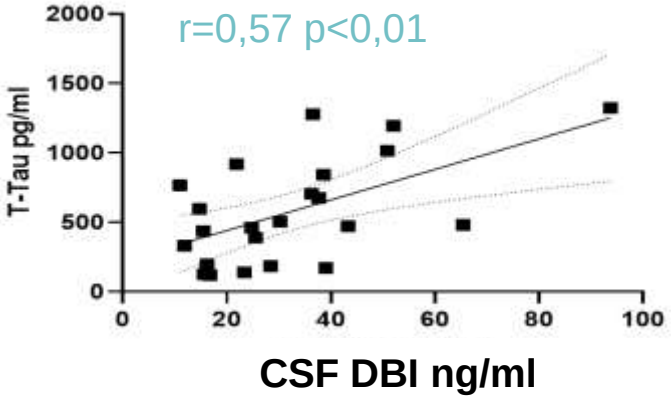
Values are expressed in pmol/ml.

* $p \leq 0.05$.
† $p \leq 0.01$.
‡ $p \leq 0.001$ vs controls.

Correlation between CSF and serum DBI
unpublished data



DBI levels in CSF correlate with marker of neurodegeneration
Evaluation of T-Tau (unpublished results)

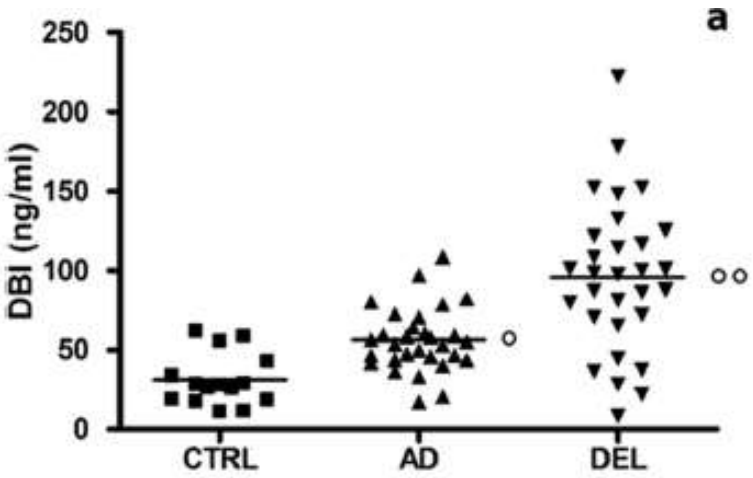


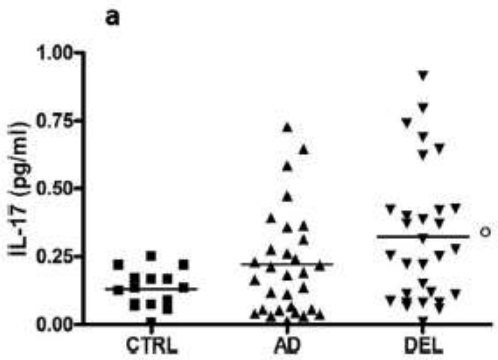
Neurological Sciences (2021) 42:1003–1007
https://doi.org/10.1007/s10072-020-04608-x

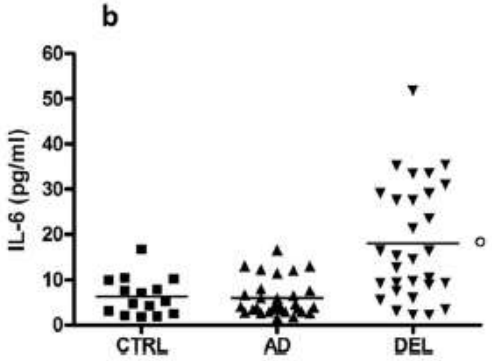
ORIGINAL ARTICLE

Serum DBI and biomarkers of neuroinflammation in Alzheimer's disease and delirium

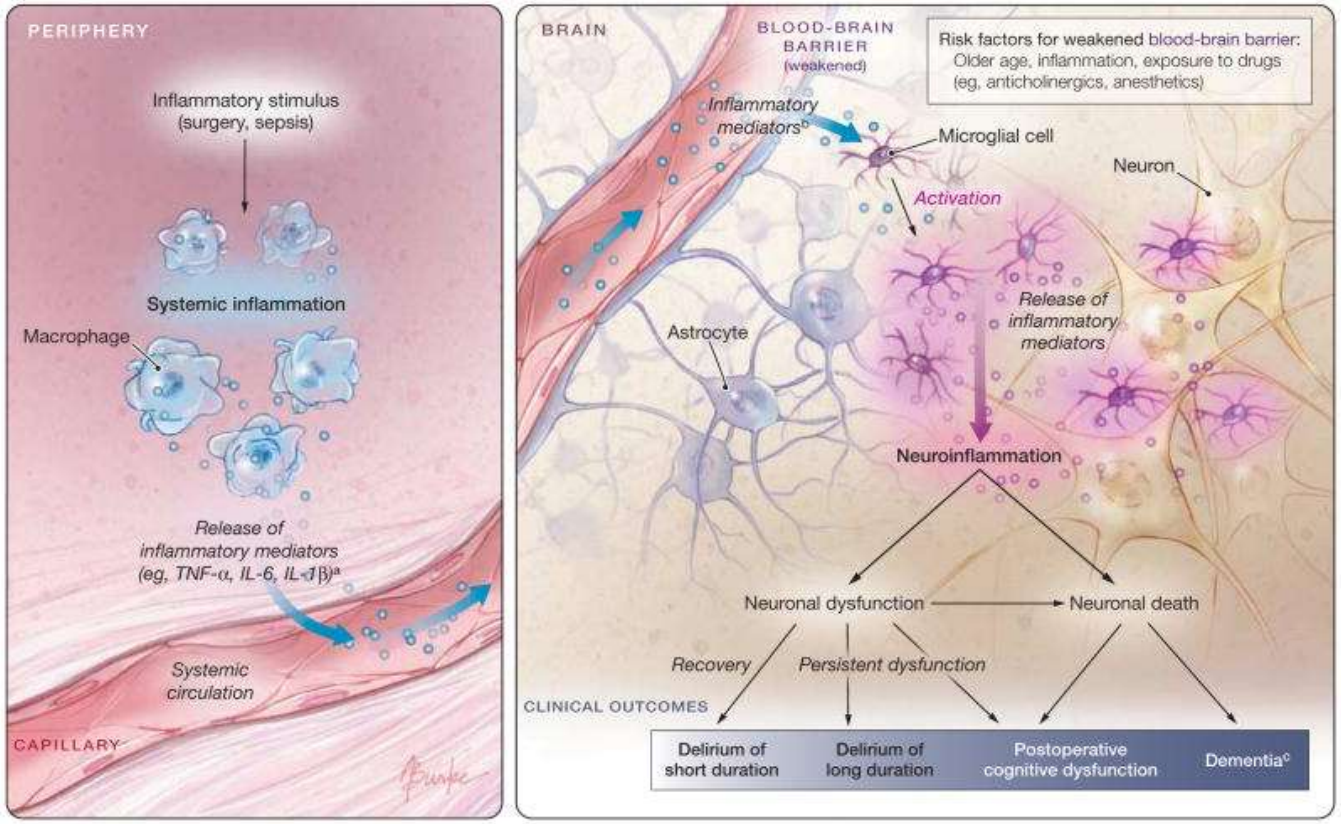
Elisa Conti[1] · Simona Andreoni[1] · Davide Tomaselli[1] · Benedetta Storti[1,2] · Francesco Brovelli[1,2] · Roberto Acampora[1,2] · Fulvio Da Re[1,2] · Ildebrando Appollonio[1,2] · Carlo Ferrarese[1,2] · Lucio Tremolizzo[1,2]







Inflammatory model of Delirium



Inflammatory Model of the Pathophysiology of Postoperative Delirium

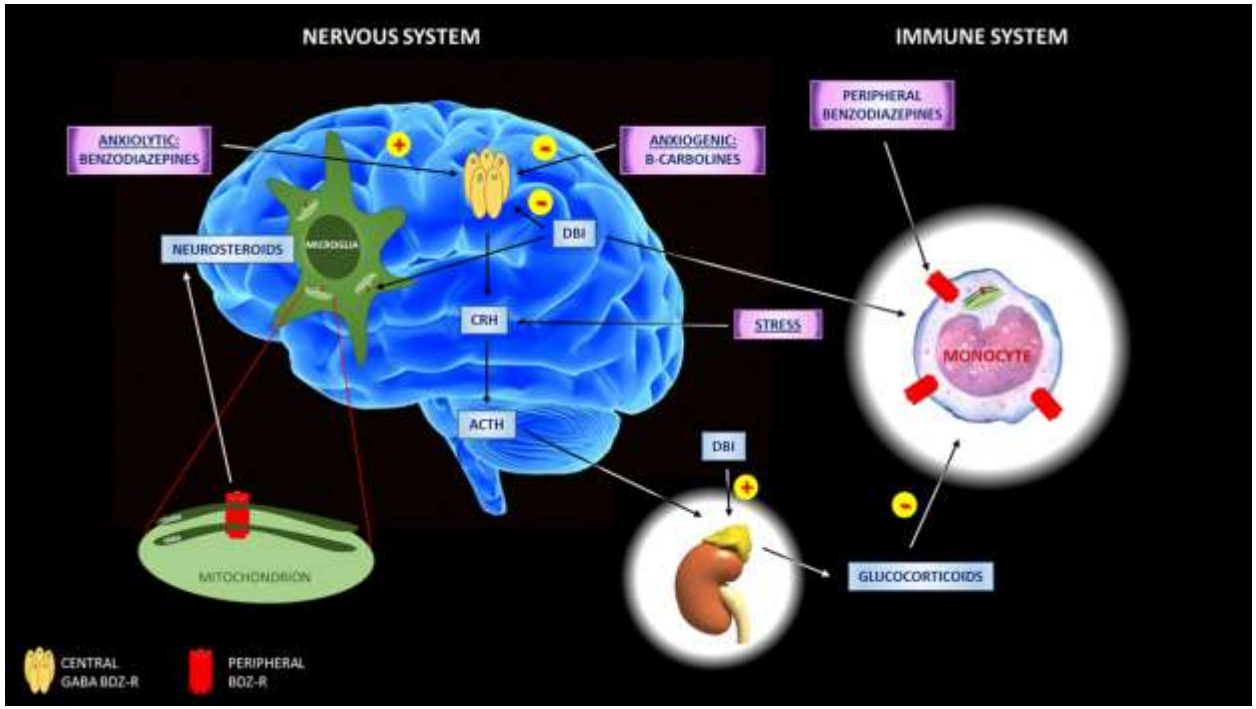
JAMA, July 4, 2012—Vol 308, No. 1

interplay of CNS and periphery in neuroinflammation

lymphomonocytes play a central role in: cytokines and anti Abeta Ab production, Abeta phagocytosis and chemotaxis

DBI/TSPO as key players in CNS/peripheral links

Peripheral biomarkers as new tools for personalized medicine



New therapeutic strategies

- **Anti-amyloid drugs:**

  decrease production*: enzymatic inhibitors*

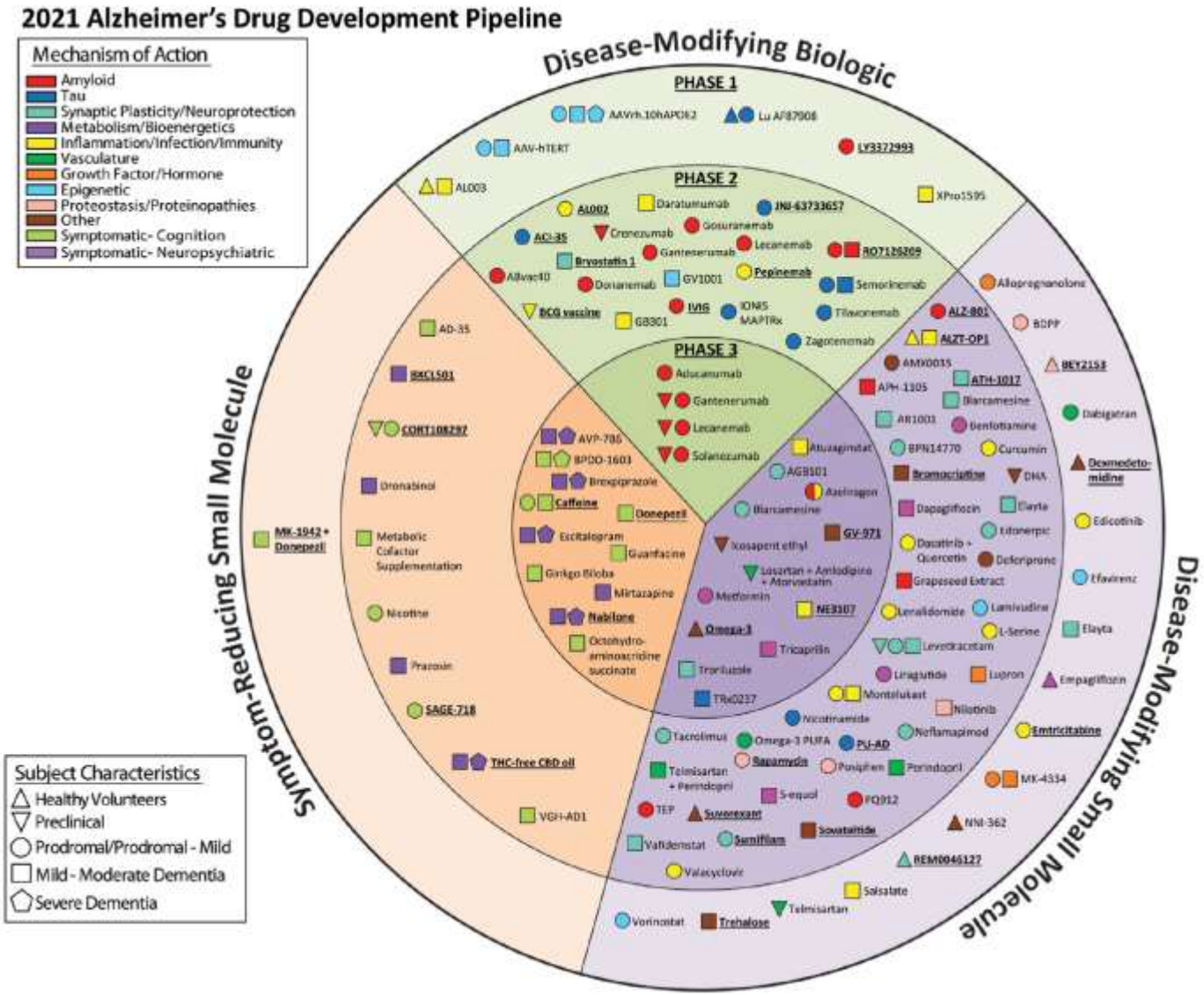
  removal: *immunotherapy*

- **Anti-TAU drugs**
- **Anti-inflammatory strategies**

Alzheimer's disease drug development pipeline: 2021

Alzheimer's Dement. 2021;7:e12179.
https://doi.org/10.1002/trc2.12179

Jeffrey Cummings[1] | Garam Lee[2] | Kate Zhong[3] | Jorge Fonseca[4] | Kazem Taghva[4]



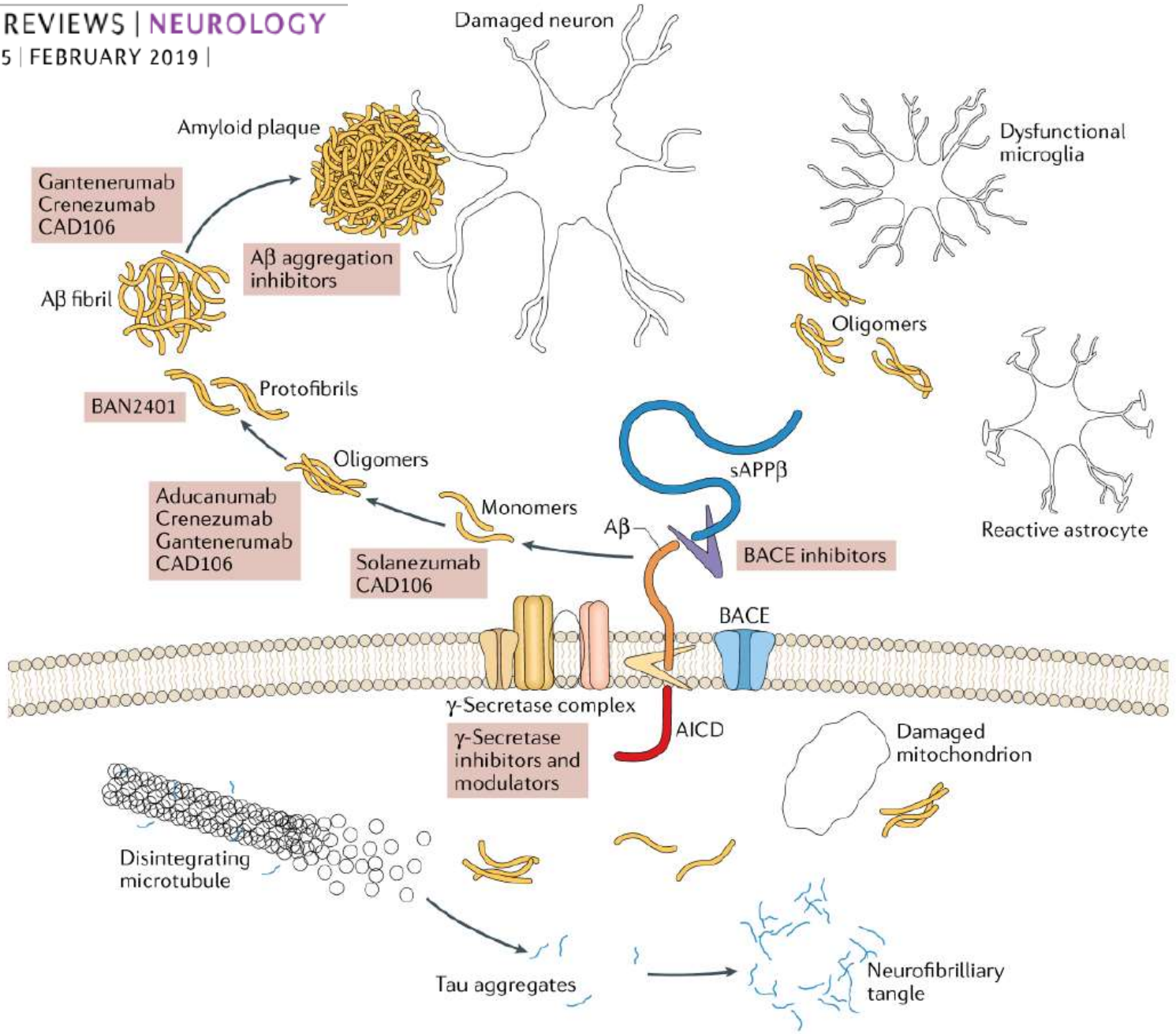
Beginning of anti amyloid strategies

- **1999** Transgenic mice immunized with Aβ1-42 display reduced plaque burden *(Schenck et al, Nature 1999)*
- **2000** Immunized mice display better cognitive performance *(Janus et al.,; Morgan et al., Nature 2000)*
- **2001** Phase I trial: no adverse reactions after single injection of AN-1792.
- **2002** Phase II trial on 372 patients: stopped for meningo-encephalites in 18 (6%) patients

Passive immunization

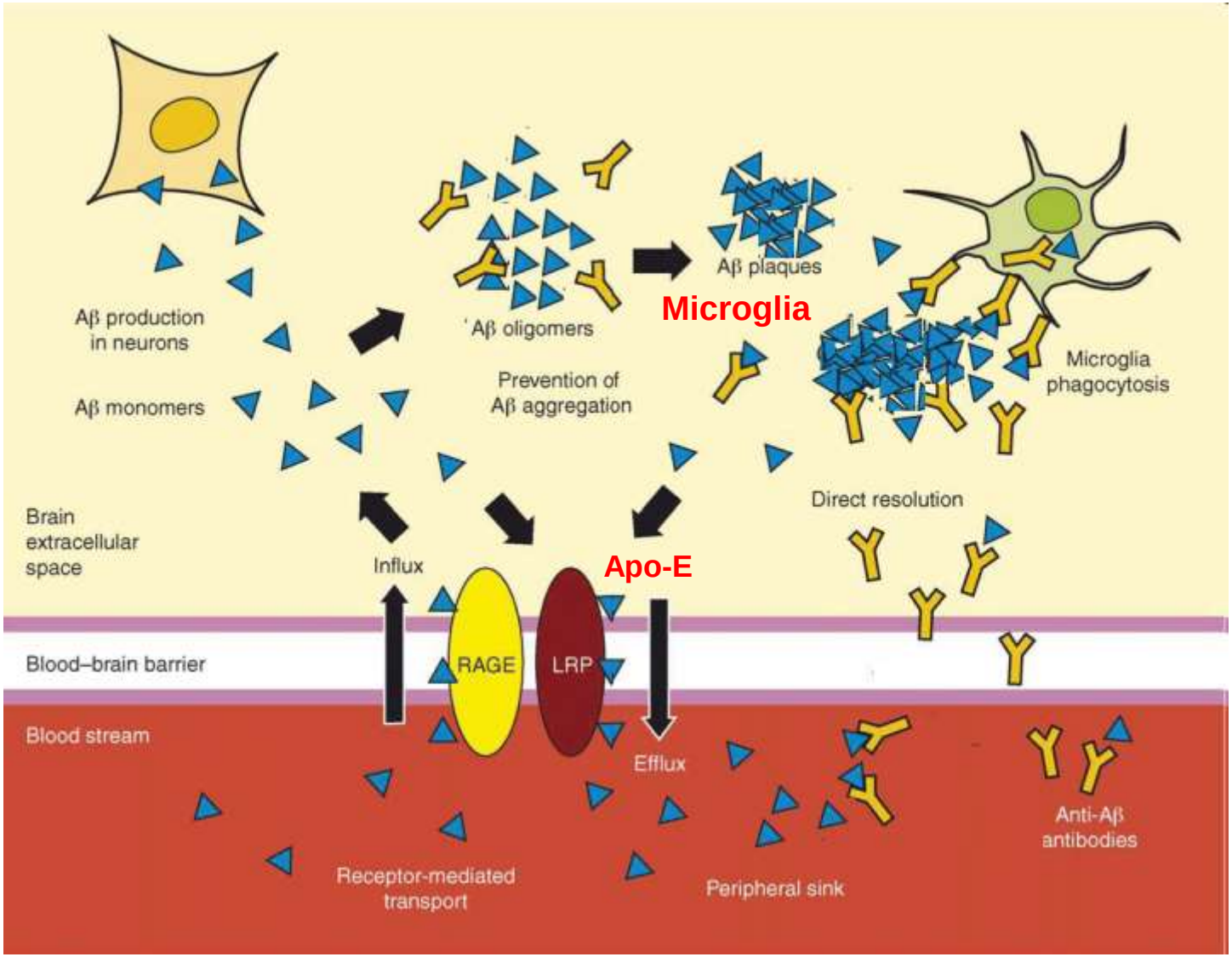
- Bapineuzumab (Pfizer): *binds N-terminal Abeta epitope*, mainly fibrils and plaques
- Solaneuzumab (Lilly): *binds mid-domain Abeta epitope*, only soluble monomers
- Gantenerumab (Roche): *binds N-terminal and mid-domain* Abeta, mainly fibrils
- Crenezumab (Genentech-Roche): *binds N-terminal and mid-domain* Abeta, mainly oligomers
- Aducanumab (Biogen): *binds N-terminal Abeta*, fibrils and oligomeric forms
- BAN 2401(EISAI): *binds preferentially* protofibrils and fibrils, with low affinity for monomers and oligomers

NATURE REVIEWS | NEUROLOGY
VOLUME 15 | FEBRUARY 2019 |



A critical appraisal of amyloid-beta-targeting therapies for Alzheimer disease

Francesco Panza[1,2,5,*], Madia Lozupone[1], Giancarlo Logroscino[1,2] and Bruno P. Imbimbo[4,5]

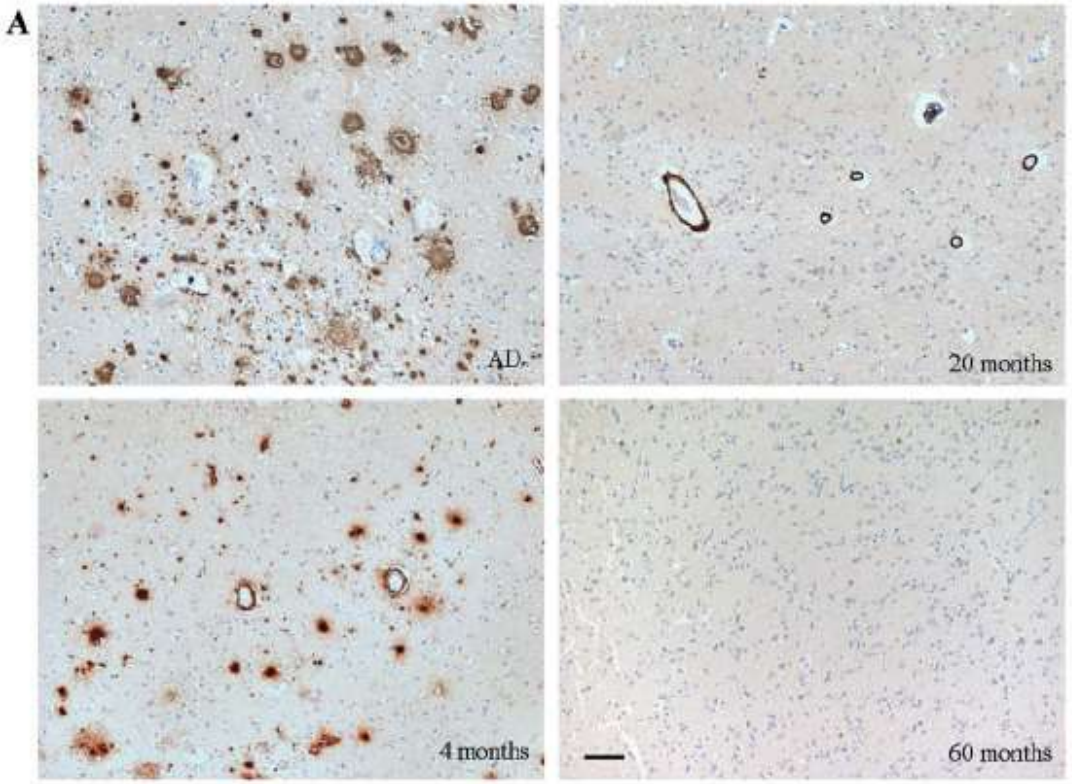

Aβ production
in neurons
Aβ monomers
Aβ oligomers
Aβ plaques
Microglia
Prevention of
Aβ aggregation
Microglia
phagocytosis
Direct resolution
Brain
extracellular
space
Influx
Apo-E
Blood–brain barrier
RAGE
LRP
Blood stream
Efflux
Anti-Aβ
antibodies
Receptor-mediated
transport
Peripheral sink

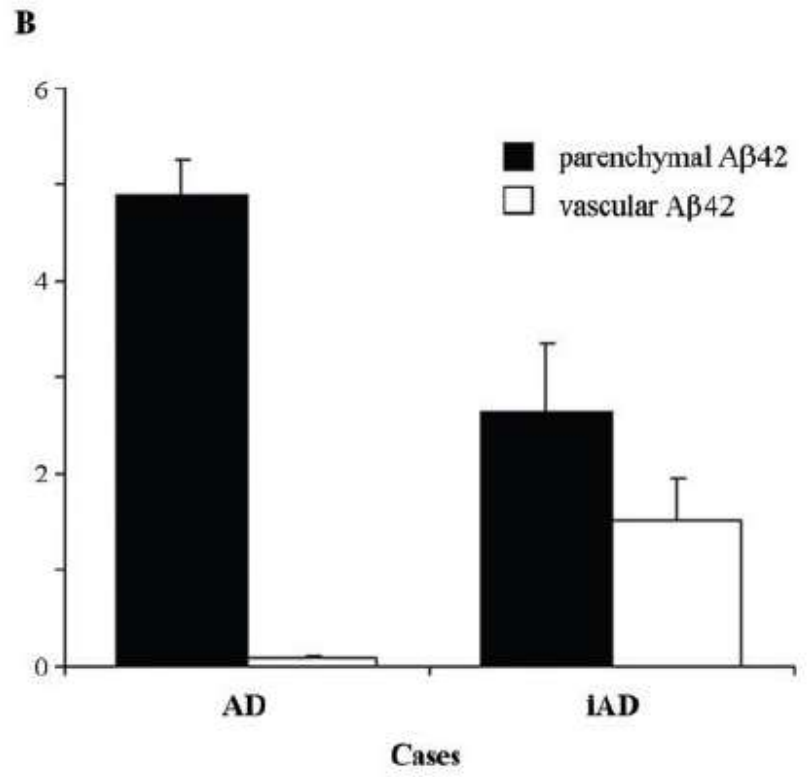
doi:10.1093/brain/awn261 *Brain* (2008), **131**, 3299–3310

Consequence of Aβ immunization on the vasculature of human Alzheimer's disease brain

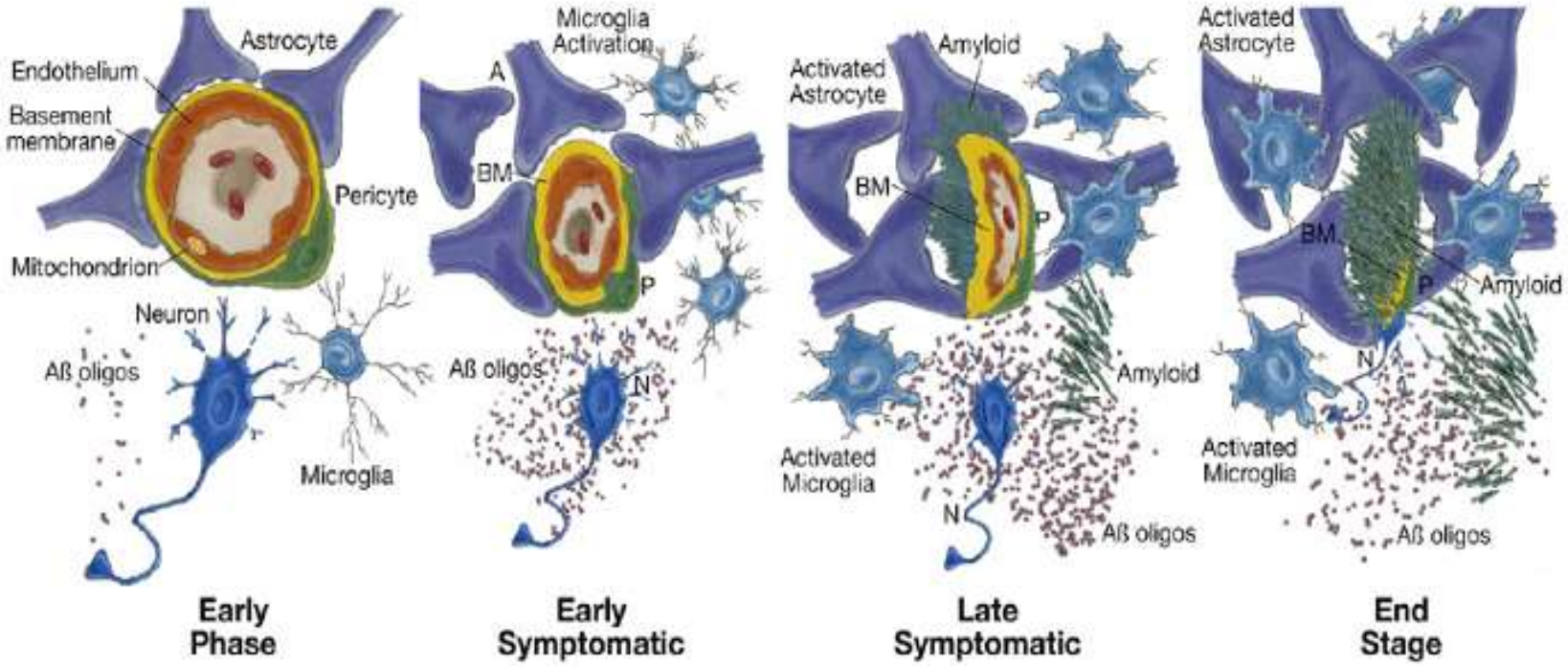
D. Boche,[1] E. Zotova,[1] R. O. Weller,[1] S. Love,[2] J. W. Neal,[3] R. M. Pickering,[4] D. Wilkinson,[5] C. Holmes[1,5] and J. A. R. Nicoll[1,6]

from the cerebral vasculature. The findings are consistent with the hypothesis that Aβ immunization results in solubilization of plaque Aβ42 which, at least in part, exits the brain via the perivascular pathway, causing a transient increase in the severity of CAA. The extent to which these vascular alterations following Aβ immunization in Alzheimer's disease are reflected in changes in cognitive function remains to be determined.





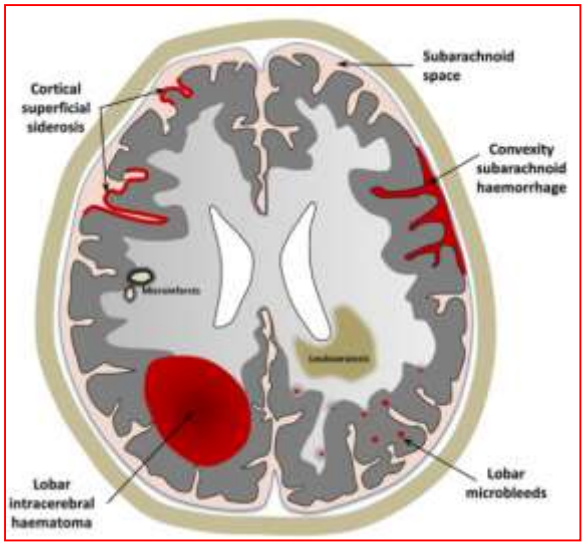
the Neurovascular damage

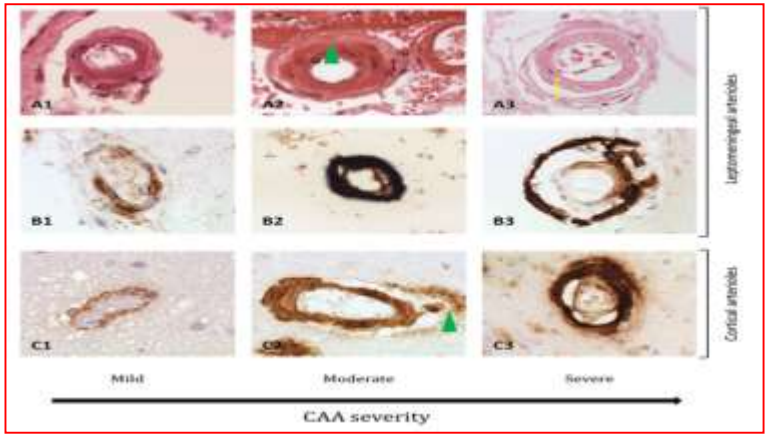


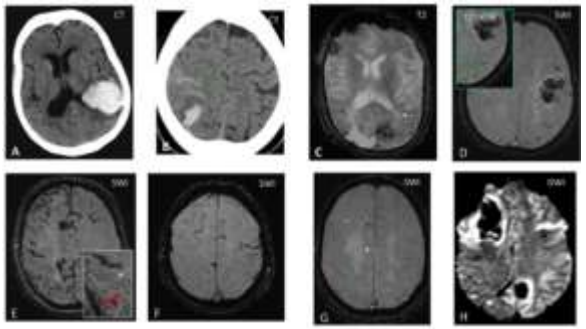
CEREBRAL AMYLOID ANGIOPATHY

CORRELATES OF CAA

- Major Haemorrage(s) (lobar or cortical-subcortical) (MH)
- Multiple Cerebral Microbleeds (CMB)
- Convexity Subarachnoid Haemorrhage (SAH)
- Cortical Superficial Siderosis (CSS)
- **CAA-RI (related inflammation)**

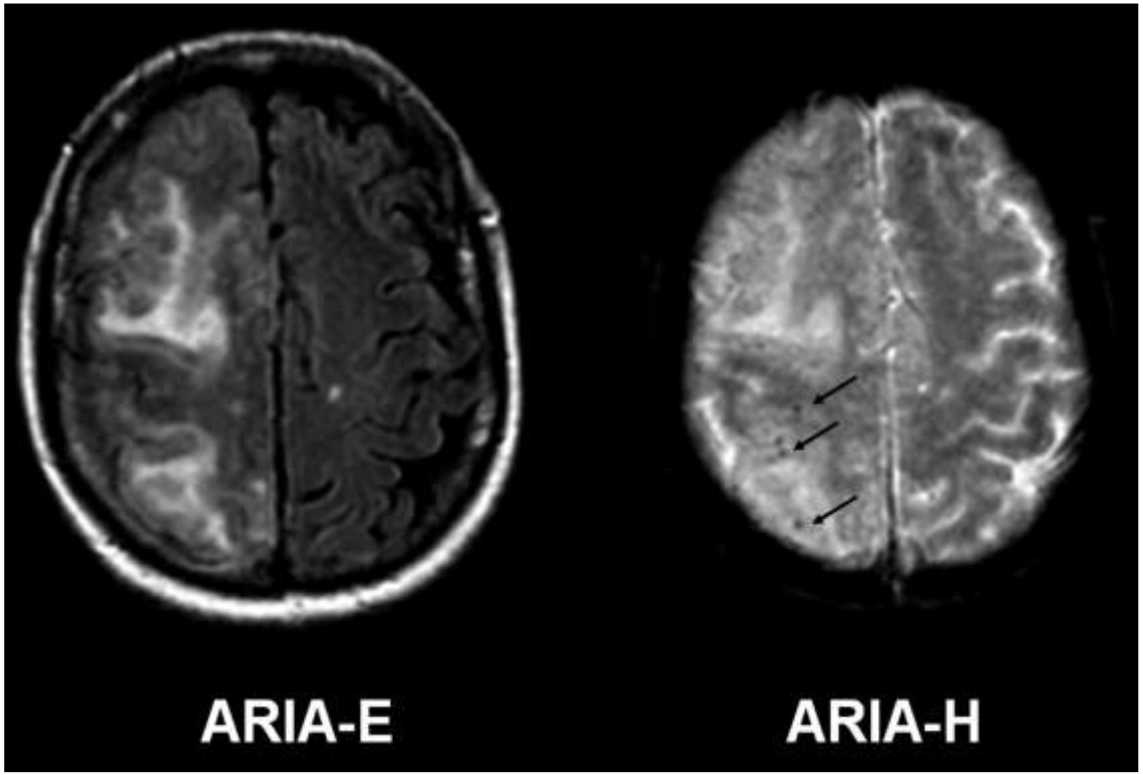






Adverse effects of Abeta immunization: Amyloid Related Imaging Abnormalities (ARIA)

Brain Edema (ARIA-E) **Brain Hemorrhage (ARIA-H)**



ANNALS of Neurology
THE OFFICIAL JOURNAL OF THE AMERICAN NEUROLOGICAL ASSOCIATION AND THE CHILD NEUROLOGY SOCIETY

EDITORIAL

Inflammatory Cerebral Amyloid Angiopathy and Amyloid-Modifying Therapies: Variations on the Same ARIA?

David J. Werring, FRCP

Stroke Research Group, Department of Brain Repair and Rehabilitation, University College London Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, United Kingdom

Reisa Sperling, MD

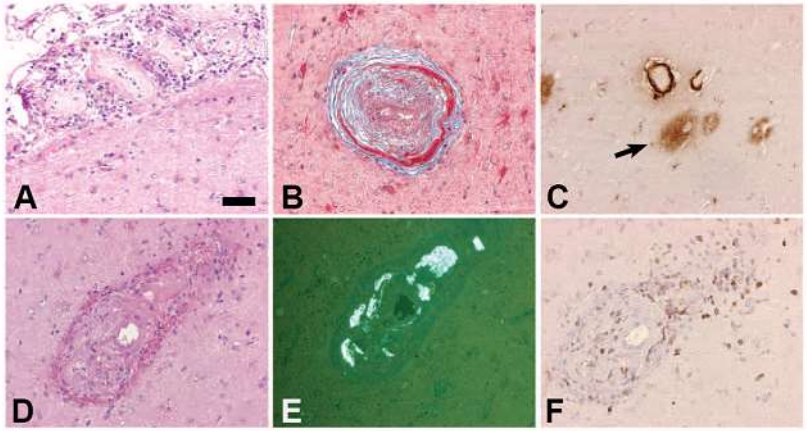
Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA

ANNALS of Neurology
THE OFFICIAL JOURNAL OF THE AMERICAN NEUROLOGICAL ASSOCIATION AND THE CHILD NEUROLOGY SOCIETY

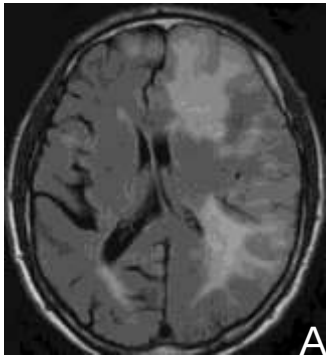
Anti–Amyloid β Autoantibodies in Cerebral Amyloid Angiopathy–Related Inflammation: Implications for Amyloid-Modifying Therapies

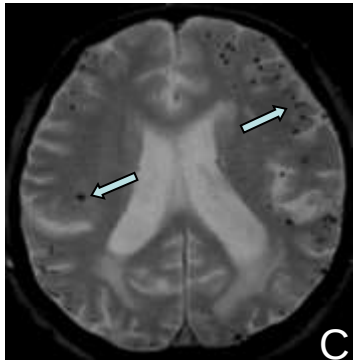
Fabrizio Piazza, PhD,[1] Steven M. Greenberg, MD, PhD,[2] Mario Savoiardo, MD,[3] Margherita Gardinetti, MD,[1] Luisa Chiapparini, MD,[3] Irina Raicher, MD,[4] Ricardo Nitrini, MD,[4] Hideya Sakaguchi, MD,[5] Monica Brioschi, MD,[6] Giuseppe Billo, MD,[7] Antonio Colombo, MD,[8] Francesca Lanzani, MD,[8] Giuseppe Piscosquito, MD,[9] Maria Rita Carriero, MD,[9] Giorgio Giaccone, MD,[10] Fabrizio Tagliavini, MD,[10] Carlo Ferrarese, MD, PhD,[1] and Jacopo C. DiFrancesco, MD, PhD[1]

F Piazza et al. Ann Neurol. 2013 Feb 11

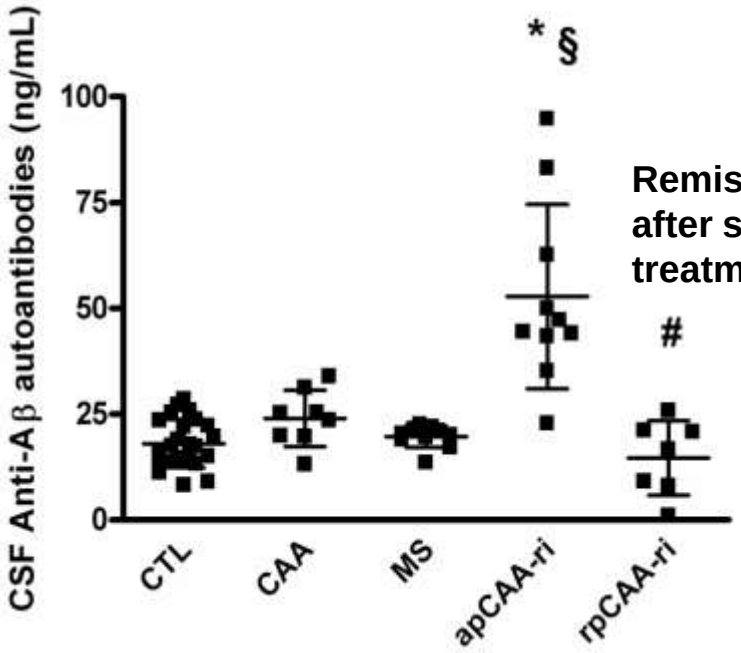


acute phase (FLAIR) **Microhaemorrhages (T2*)**





Acute phase



Remission after steroid treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

EDITORIALS

N ENGL J MED 370; JANUARY 23, 2014: 377

Antiamyloid Therapy for Alzheimer's Disease — Are We on the Right Road?

Eric Karran, Ph.D., and John Hardy, Ph.D.

PROBLEMS WITH ANTI-AMYLOID THERAPIES AND NEW STRATEGIES

1. Too late ?: lack of efficacy in demented patients
   - ➡ treat earlier: prodromal (MCI) or preclinical AD (DIAN, A4 and API trials)

2. Too little ?: not enough drug for side effects
   - ➡ dose escalation and dose adjustments
   - Increase brain penetration by nanoparticles?

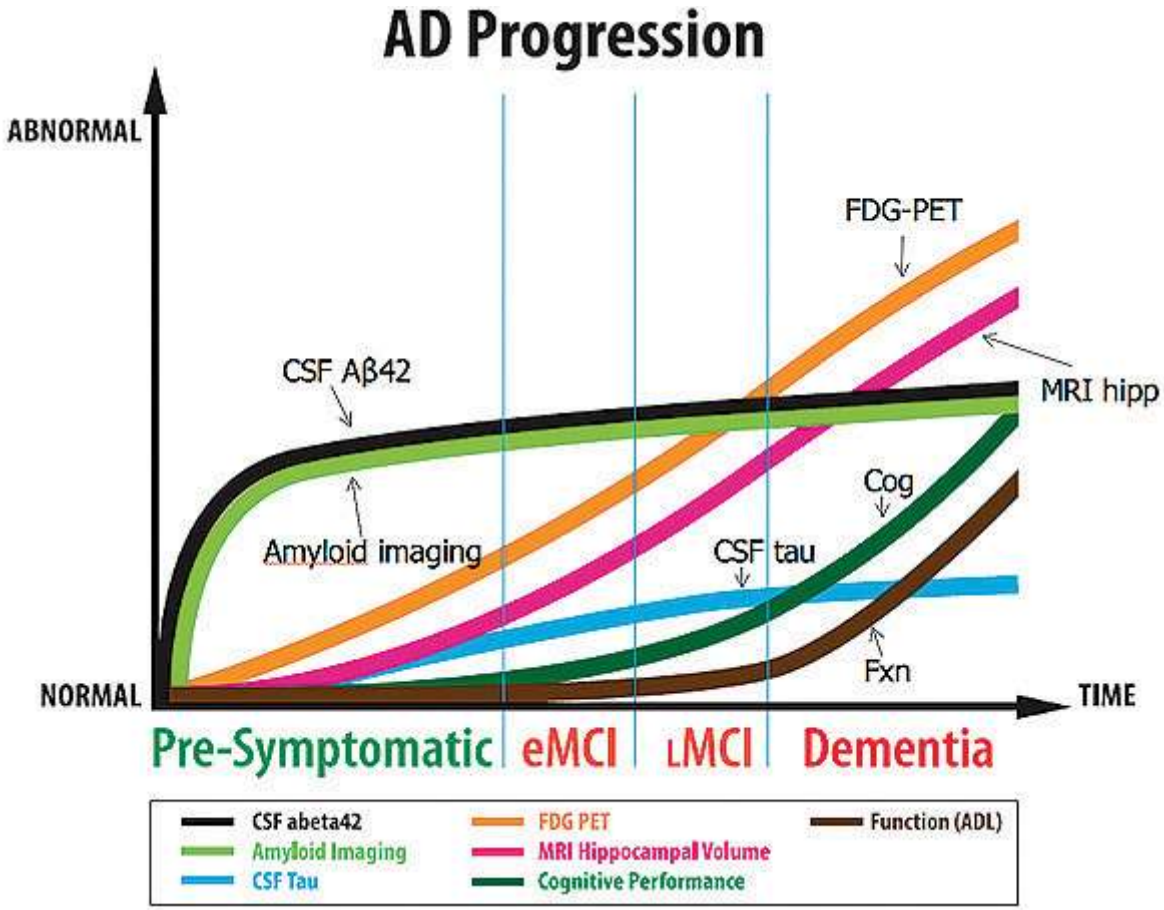
2. Right patient target ? : not AD patients
   - ➡ select biomarker positive by PET and CSF

Alzheimer's disease pathology is thought to begin 15–20 years before clinical presentation

- AD pathologic changes in the brain start 15–20 years before the development of symptoms[3,4]
- AD is now considered a continuum, consisting of a preclinical stage and progressing to AD dementia[3]
- Disease-modifying therapies aiming to interfere with the underlying pathophysiologic mechanisms of the disease process that lead to cell death may need to be initiated early in the course of disease[4]

*Please note that the placement of symptoms around the image do not correspond to specific regions of the brain
Aβ, amyloid beta; AD, Alzheimer's disease

1. Mathur R, et al. PLoS One 2015;10:e0118463; 2. Day RJ, et al. PLoS One 2015;10:e0132637;
3. Jack CR, et al. Alzheimers Dement 2018;14:535–562; 4. Bateman RJ, et al. N Engl J Med 2012;367:795–804


AD Progression
ABNORMAL
NORMAL
TIME
FDG-PET
MRI hipp
CSF Aβ42
Amyloid imaging
Cog
CSF tau
Fxn
Pre-Symptomatic
eMCI
LMCI
Dementia
CSF abeta42
Amyloid Imaging
CSF Tau
FDG PET
MRI Hippocampal Volume
Cognitive Performance
Function (ADL)

Alzheimer Disease (AD) vs Alzheimer Dementia

Preclinical AD

The long asymptomatic period between the first brain lesions and the first appearance of symptoms and which concerns normal individuals that later fulfil AD diagnostic criteria

Prodromal AD

The symptomatic predementia phase of AD, generally included in the mild cognitive impairment category; this phase is characterised by symptoms not severe enough to meet currently accepted diagnostic criteria for AD

AD dementia

The phase of AD where symptoms are sufficiently severe to meet currently accepted dementia and AD diagnostic criteria

CLINICAL-BIOMARKERS CONSTRUCT

3-class categorization: ATN biomarker

- B-amyloid plaques or assoc. pathophysiology (A) - specific
  - CSF Ab 42 (low), or better low 42/40 ratio
  - Amyloid PET
- Aggregated tau or assoc. pathophysiology (T) - specific
  - CSF phosphorylated tau (high)
  - Tau PET
- Neuronal injury and neurodegeneration (N) – non specific
  - Structural MRI
  - FDG PET
  - CSF total tau (high)

VIEWS & REVIEWS

A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers

OPEN

Clifford R. Jack, Jr., MD
David A. Bennett, MD
Kaj Blennow, MD, PhD
Maria C. Carrillo, PhD
Howard H. Feldman, MD
Giovanni B. Frisoni, MD
Harald Hampel, MD, PhD
William J. Jagust, MD
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Philip Scheltens, MD, PhD
Reisa A. Sperling, MD
Bruno Dubois, MD, PhD

ABSTRACT

Biomarkers have become an essential component of Alzheimer disease (AD) research and

A-T-(N)-	• Normal Alzheimer's biomarkers
A+T-(N)-	• Alzheimer's pathologic change
A+T+(N)-	• Alzheimer's disease
A+T+(N)+	• Alzheimer's disease
A+T-(N)+	• Alzheimer's and suspected non-Alzheimer's pathologic change
A-T+(N)-	• Non-Alzheimer's pathologic change
A-T-(N)+	• Non-Alzheimer's pathologic change
A-T+(N)+	• Non-Alzheimer's pathologic change

Alzheimer's continuum

Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group

Lancet Neurol 2021

Published Online
April 29, 2021

Bruno Dubois, Nicolas Villain*, Giovanni B Frisoni, Gil D Rabinovici, Marwan Sabbagh, Stefano Cappa, Alexandre Bejanin, Stéphanie Bombois, Stéphane Epelbaum, Marc Teichmann, Marie-Odile Habert, Agneta Nordberg, Kaj Blennow, Douglas Galasko, Yaakov Stern, Christopher C Rowe, Stephen Salloway, Lon S Schneider, Jeffrey L Cummings, Howard H Feldman*

	NINCDS-ADRDA (1984)[3]	IWG (2007)[4]	IWG (2010)[5]	NIA-AA (2011)[6,7]	IWG (2014)[8]	IWG-AA (2016)[9]	NIA-AA (2018)[10]	IWG (2021)
Applicable settings	Research and clinical	Research	Research	Research and clinical	Research	Research	Research	Research and clinical
Clinical requirements	Dementia (memory changes and another cognitive impairment)	Amnestic syndrome of a hippocampal type	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural-frontal variant	Mild cognitive impairment (amnestic or non-amnestic) or dementia	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural-frontal variant	None	None	Amnestic variant, posterior cortical atrophy, logopenic variant primary progressive aphasia, behavioural or dysexecutive frontal variant, corticobasal syndrome, semantic and nonfluent variants of primary progressive aphasia*
Biological requirements	None	CSF biomarkers, MRI atrophy, ^{18}F-fluorodeoxyglucose PET hypometabolism, amyloid PET positive, or Alzheimer's disease autosomal dominant mutation	Pathophysiological markers: CSF changes (low CSF Aβ42, high phosphorylated tau, or high total tau) or amyloid PET positive	Amyloid β marker (CSF or PET) or marker of degeneration (CSF tau, phosphorylated tau, ^{18}F-fluorodeoxyglucose-PET, and T1-weighted MRI)	CSF amyloid β and tau or amyloid PET positive	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)

ADRDA=Alzheimer's Disease and Related Disorders Association (now the Alzheimer's Association) Work Group. IWG=International Working Group criteria. IWG-AA=International Working Group and Alzheimer's Association joint criteria. NIA-AA=US National Institute on Aging and Alzheimer's Association joint criteria. NINCDS=US National Institute of Neurological and Communicative Disorders and Stroke criteria.
*Cognitively unimpaired individuals are considered at risk for Alzheimer's Disease.

Table 1: Details of successive proposed criteria for Alzheimer's disease diagnosis

The diagnosis of Alzheimer's disease is clinical–biological. It requires the presence of both a specific clinical phenotype of Alzheimer's disease (phenotype positive) and biomarker evidence of Alzheimer's disease pathology (amyloid-positive and tau positive).

Panel 4: Proposed stratification of risk of asymptomatic people according to biomarker results

People with absolute risk

Carriers of autosomal dominant mutations (*APP*, *PSEN1*, *PSEN2*, or trisomy 21)[106]

People with high risk

Cognitively unimpaired individuals with:

- CSF or PET that is amyloid-positive and tau positive[24–26]
- PET that is tau positive outside the limbic cortex (Braak stage 5 or higher)[107]
- *APOE* ε4 homozygosity[108]

People with undefined risk*

Cognitively unimpaired individuals with an incomplete biomarker pattern:

- Amyloid positive; tau negative or unknown[33]
- Amyloid negative; tau positive[51]

Challenges of pre-clinical trials

- Difficulty to assess the **level of risk**, subtle cognitive changes and clinical progression
- Need for **long-term follow-up** (5-10 years?)
- Need for **biochemical markers** (PET – CSF) as surrogate end-points: **related to clinical progression?**
- **Legal, Ethical and Economical problems !**

THE FUTURE IN AD TREATMENT: prevention BETTER than treatment

PERSONALISED MEDICINE

- **Biomarkers for preclinical diagnosis**
  Preclinical – Prodromal AD (MCI): level of risk assessment
- **EARLY DMD - "TARGETED" DMD**
- **DIFFERENT DRUGS AT DIFFERENT STAGES (anti-Abeta – Anti TAU – antioxidants…others?)**
- **COMBINATION THERAPIES**

WHEN? (2 - 5 – 10 – 20 YEARS ?)

For more information on this publication, visit www.rand.org/t/RR2503.

Research Report

JAKUB P. HLÁVKA, SOEREN MATTKE, JODI L. LIU

Assessing the Preparedness of the Health Care System Infrastructure in Six European Countries for an Alzheimer's Treatment

KEY FINDINGS

- The burden of Alzheimer's disease in high-income countries is expected to approximately double between 2015 and 2050. Recent clinical trial results give hope that a disease-modifying therapy might become available in the near future. The therapy is expected to treat early-stage patients to prevent or delay the progression to dementia.
- This preventive treatment paradigm implies the need to screen, diagnose, and treat a large population of patients with mild cognitive impairment. There would be many undiagnosed prevalent cases that would need to be addressed initially, and then the longer-term capacity to address incident cases would not need to be as high as the short-term capacity.
- We use a simulation model to assess the preparedness of the health care system infrastructure in six European countries—France, Germany, Italy, Spain, Sweden, and the United Kingdom—to evaluate, diagnose, and treat the expected number of patients.
- Projected peak wait times range from five months for treatment in Germany to 19 months for evaluation in France. The first years without wait times would be 2030 in Germany and 2033 in France, and 2042 in the United Kingdom and 2044 in Spain. Specialist capacity is the rate-limiting factor in France, the United Kingdom, and Spain, and treatment delivery capacity is an issue in most of the countries.
- If a disease-modifying therapy becomes available in 2020, we estimate the projected capacity constraints could result in over 1 million patients with mild cognitive impairment progressing to Alzheimer's dementia while on wait-lists between 2020 and 2044 in these six countries.
- A combination of reimbursement, regulatory, and workforce planning policies, as well as innovation in diagnosis and treatment delivery, is needed to expand capacity and to ensure that available capacity is leveraged optimally to treat patients with early-stage Alzheimer's disease.

ITALY: EXPECTED PATIENTS AND HEALTH CARE SYSTEM CAPACITY

Millions of patients could seek diagnosis and treatment

Of the 20.6 million people age 55 and older in 2019,

16.4 MILLION could seek screening in a doctor's office

Of the 2.9 million who screen positive for MCI,

1.4 MILLION could seek a dementia specialist for evaluation (there are 9,501 neurologists, geriatricians, and geriatric psychiatrists, or 16.0 specialists per 100,000 people)

1.3 MILLION could be referred for biomarker testing

0.6 MILLION might test positive for biomarkers and return to the specialist to learn about treatment

0.5 MILLION could be recommended for infusion therapy

The primary aim of INTERCEPTOR is to identify a biomarker or a set of biomarkers able to predict with greatest accuracy, highest risks/costs ratio, lowest invasiveness and best availability on the territorial level, the conversion of diagnosis of MCI to dementia in a 3 years follow-up period.

This in order to initiate as soon as possible all those initiatives to contrast disease progression.

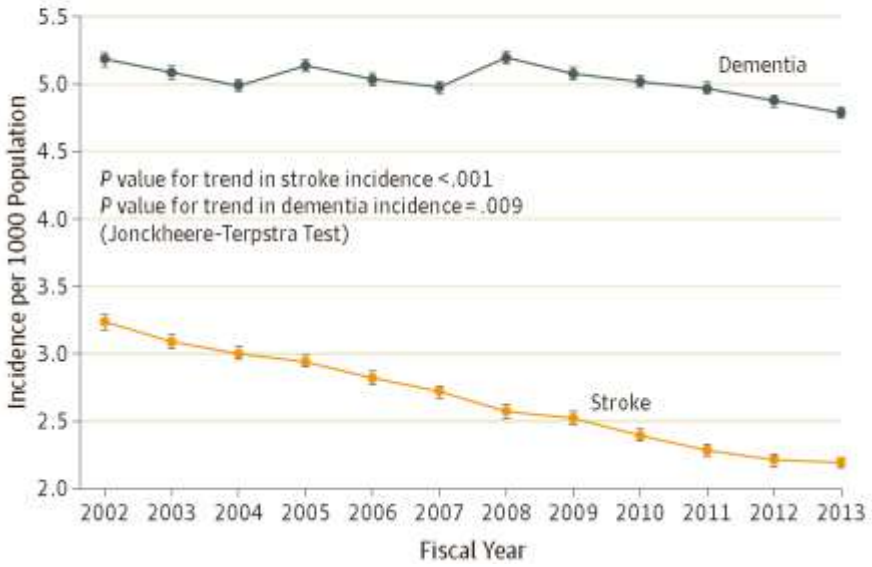
The secondary aim is to define an optimal organizational model, both in terms of transferability in clinical practice of diagnostic path defined of the primary objective and the sustainability of costs, to identify patients able to prescription of antidementia drug that now are in the course of experimentation by RCTs.

Declining Incidence of Stroke and Dementia: Coincidence or Prevention Opportunity?

Luciano A. Sposato, MD, MBA
Moira K. Kapral, MD, MSc
Jiming Fang, PhD
Sudeep S. Gill, MD, MSc
Daniel G. Hackam, MD, PhD, FRCPC
Lauren E. Cipriano, PhD
Vladimir Hachinski, CM, MD, FRCPC, DSc

JAMA Neurology December 2015 Volume 72, Number 12

Figure. Trends in Stroke and Dementia Incidence Rates, Ontario 2002-2013



A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial

www.thelancet.com Vol 385 June 6, 2015

Tiia Ngandu, Jenni Lehtisalo, Alina Solomon, Esko Levälahti, Satu Ahtiluoto, Riitta Antikainen, Lars Bäckman, Tuomo Hänninen, Antti Jula, Tiina Laatikainen, Jaana Lindström, Francesca Mangialasche, Teemu Paajanen, Satu Pajala, Markku Peltonen, Rainer Rauramaa, Anna Stigsdotter-Neely, Timo Strandberg, Jaakko Tuomilehto, Hilkka Soininen, Miia Kivipelto