

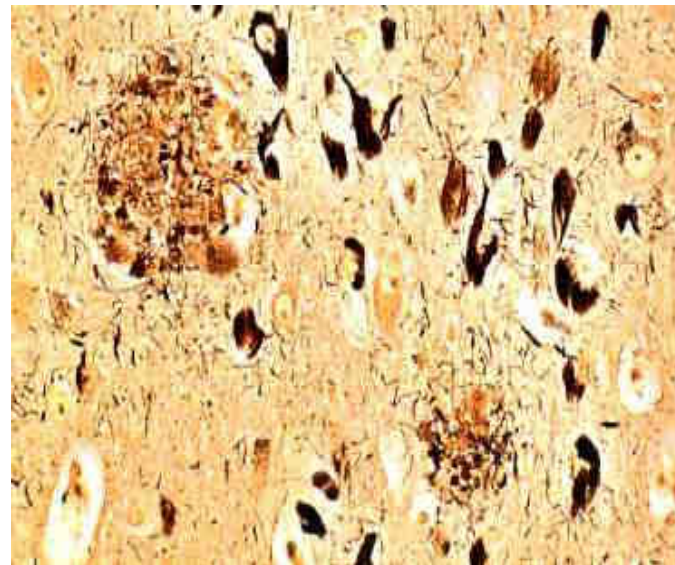
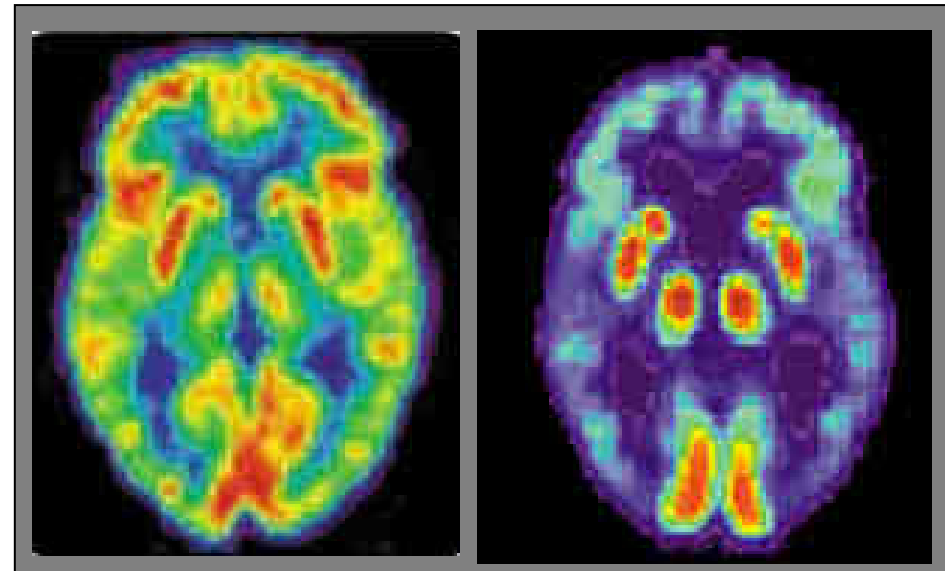
Demencia:

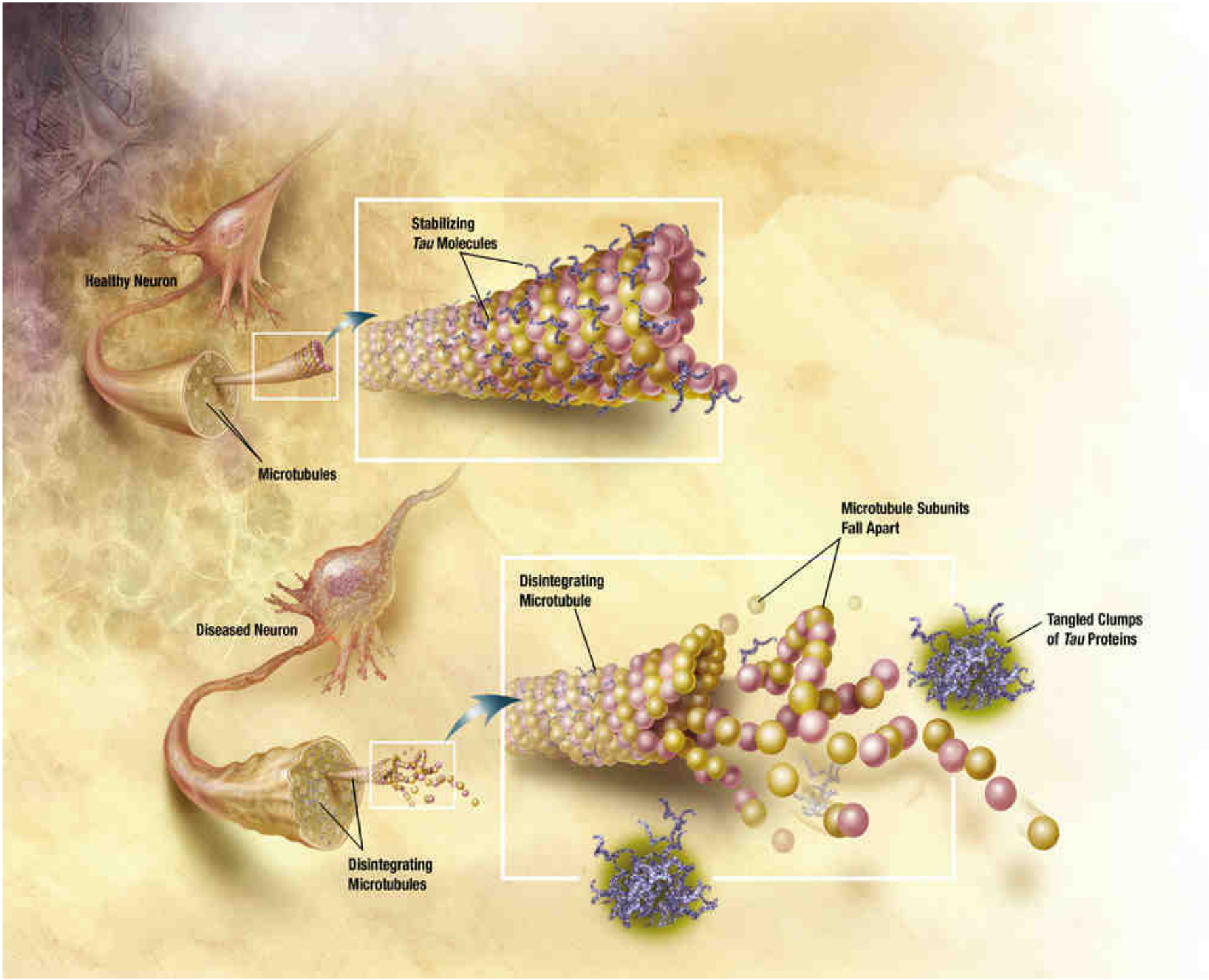
Pérdida gradual de

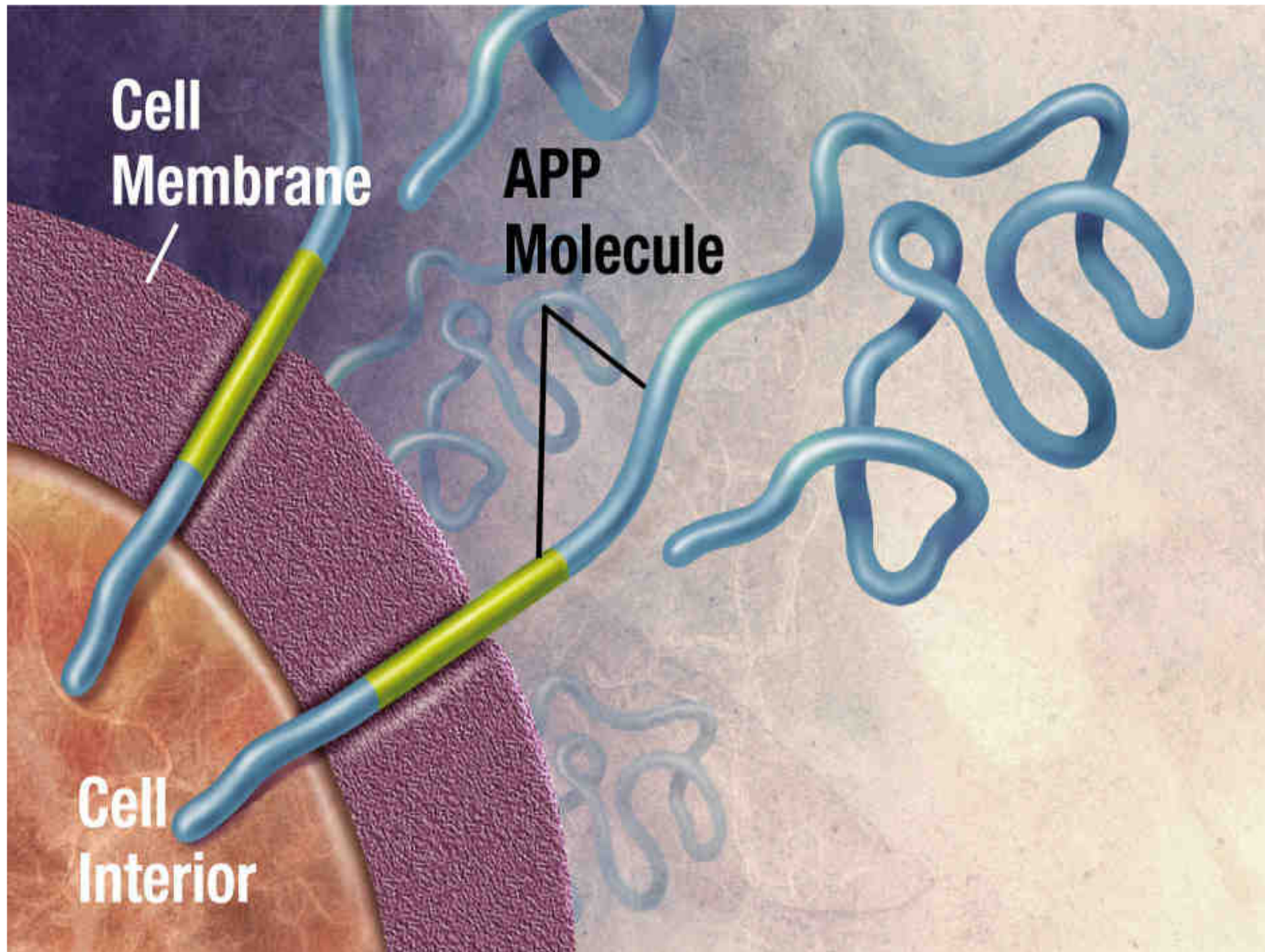
- **Memoria**

Y otras funciones cognitivas:

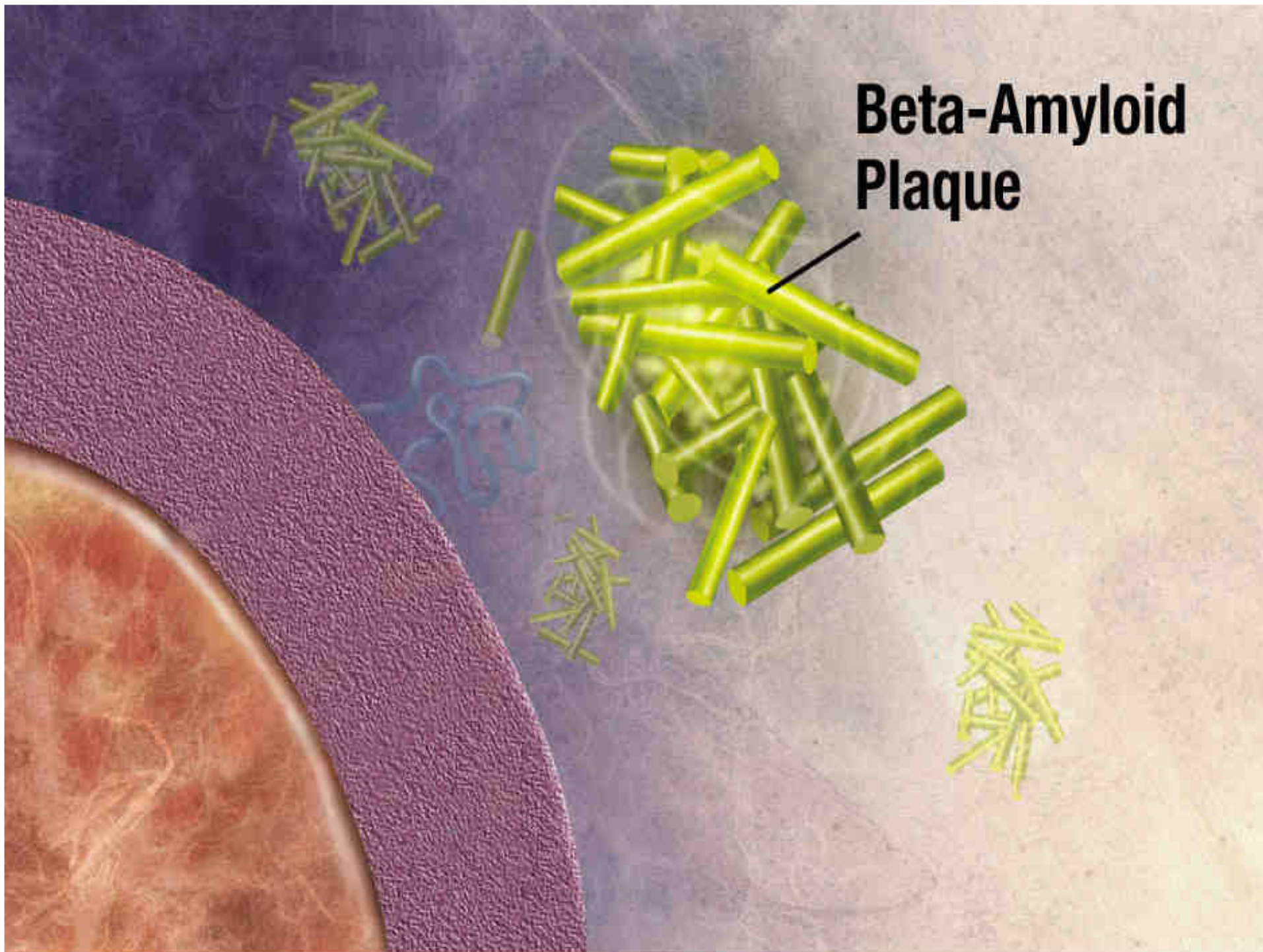
- **Lenguaje** (afasia)
- **Capacidad motora** (apraxia)
- **Percepción** (agnosia)



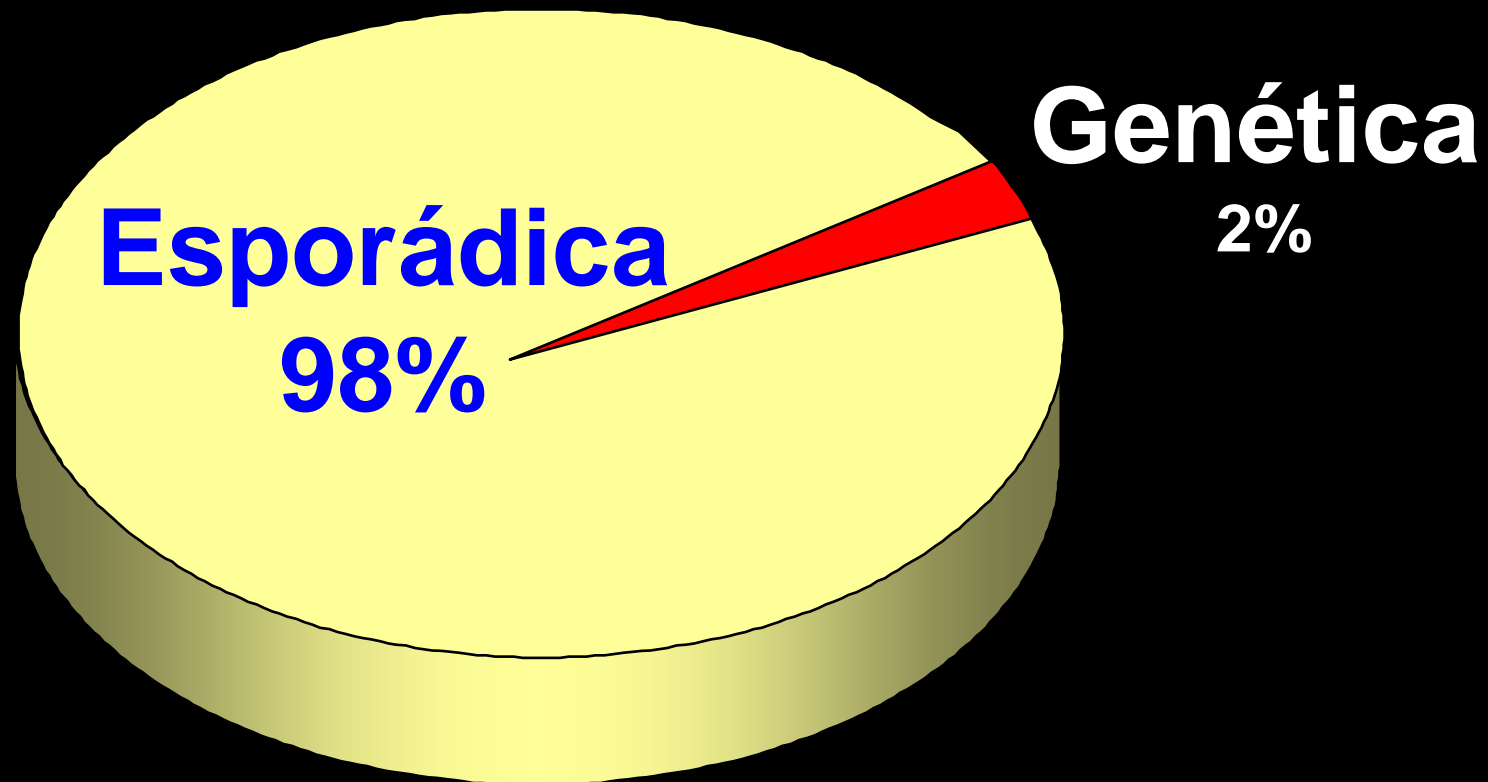


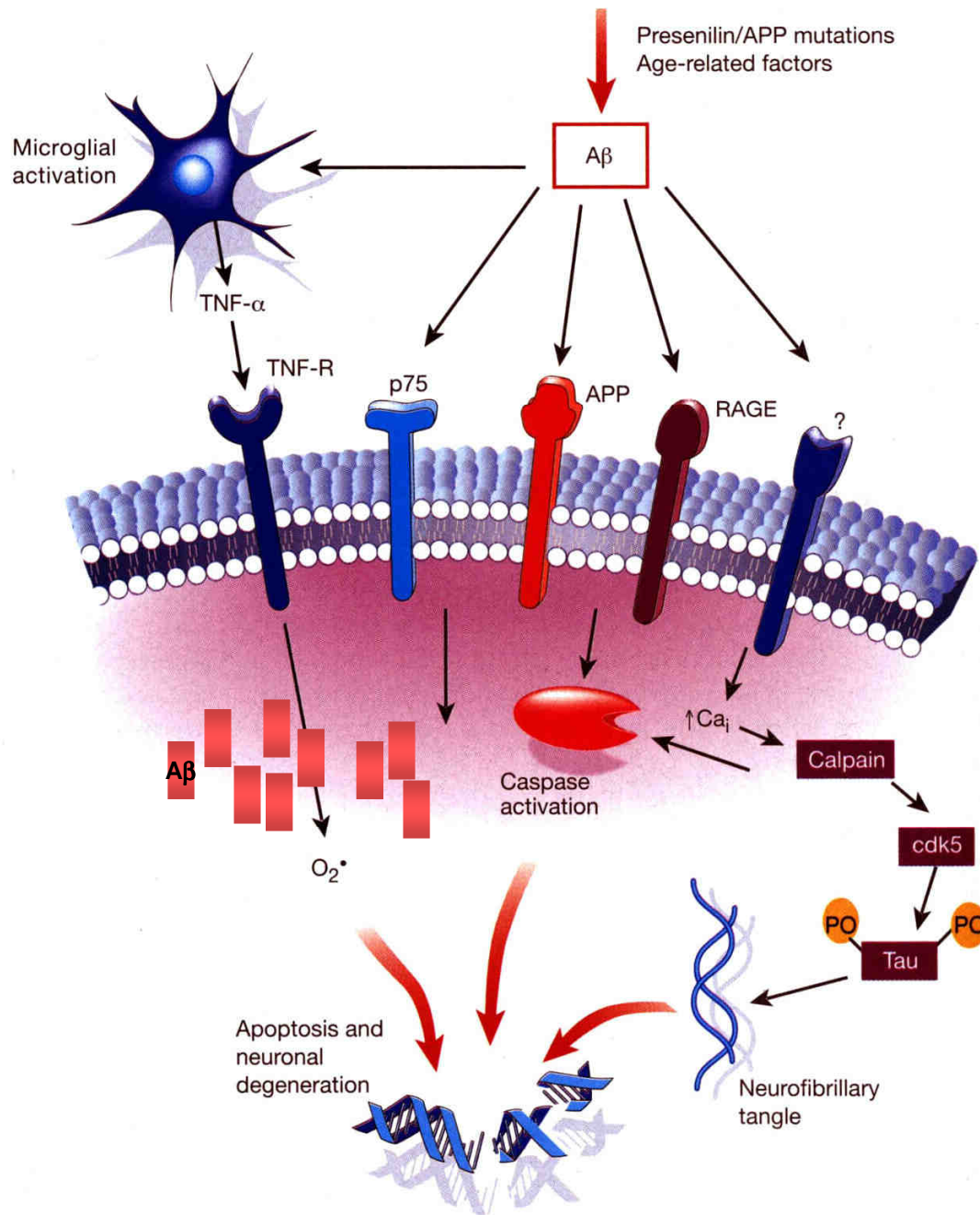


**Beta-Amyloid
Plaque**



Enfermedad de Alzheimer





NAME: Beta- & Gamma-Secretase Inhibitors

FDA PHASE: Preclinical

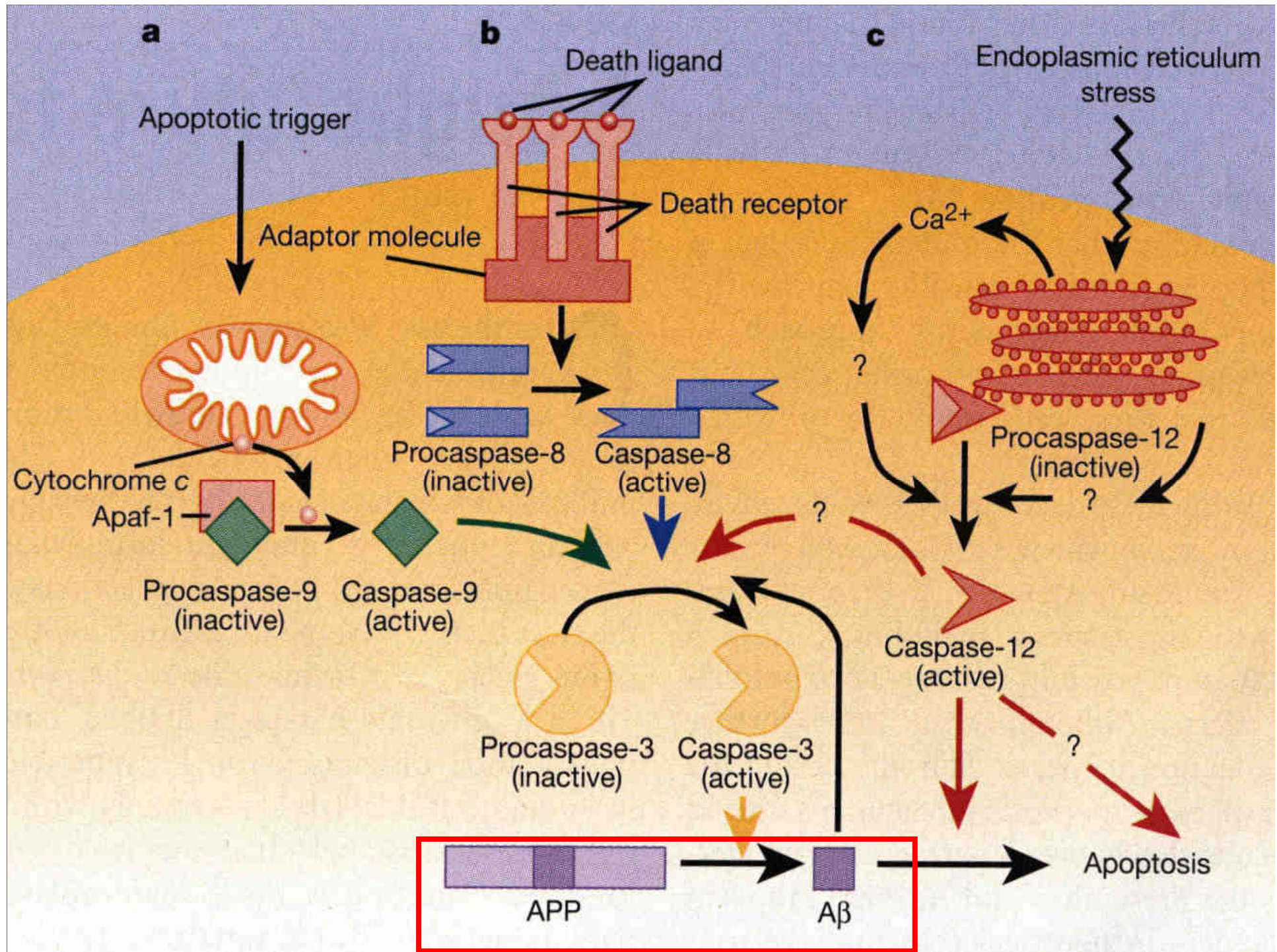
ROLE IN ALZHEIMER'S DISEASE: Inhibiting these enzymes might **reduce the burden of amyloid beta-peptide in AD patients' brains**, which might then slow the progression of the disease.

NAME: Alzhemed™

FDA PHASE: Phase III

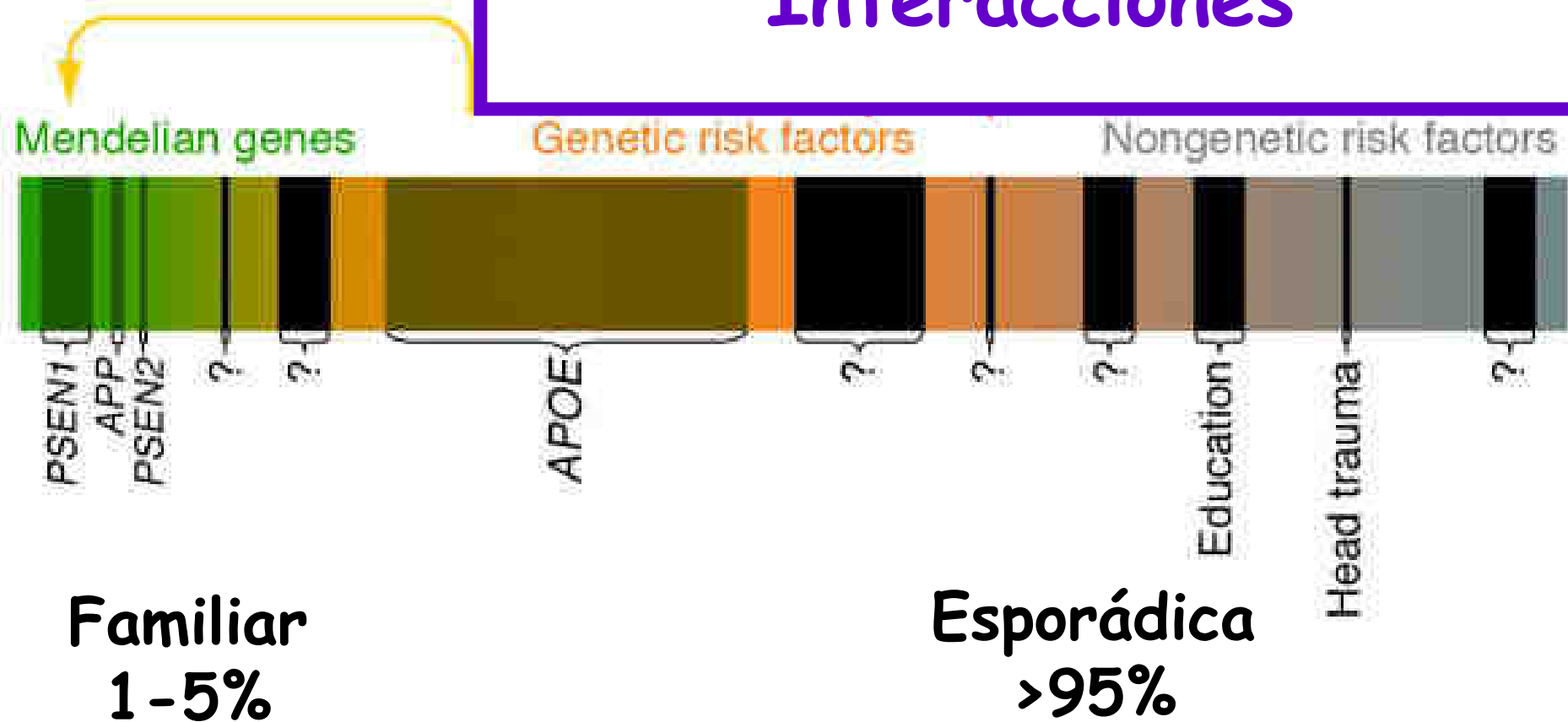
MECHANISMS: Inhibit Aβ fibrillization, binds and reduces soluble Aβ

ROLE IN ALZHEIMER'S DISEASE: Designed to **prevent amyloid formation and deposition** in the brain, and thus modify the course of AD. Alzhemed™ is expected to **act on two levels**: firstly to **prevent and stop** the formation and deposition of **amyloid fibrils** in the brain as well as to bind to soluble Aβ, and secondly to **inhibit the inflammatory response** associated with amyloid build-up in AD.



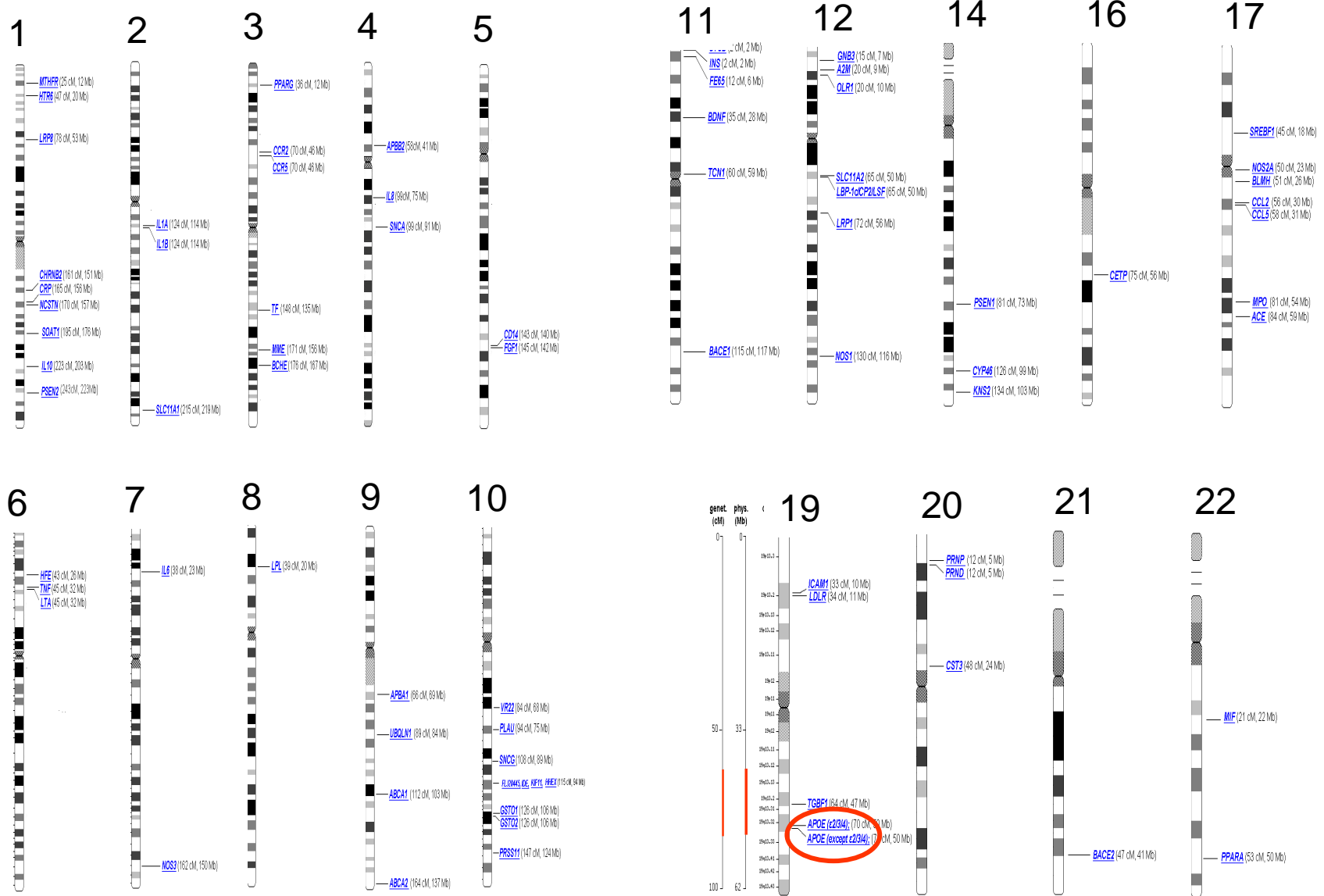
Genes y ambiente participan en la etiopatogénesis de la EA

Interacciones

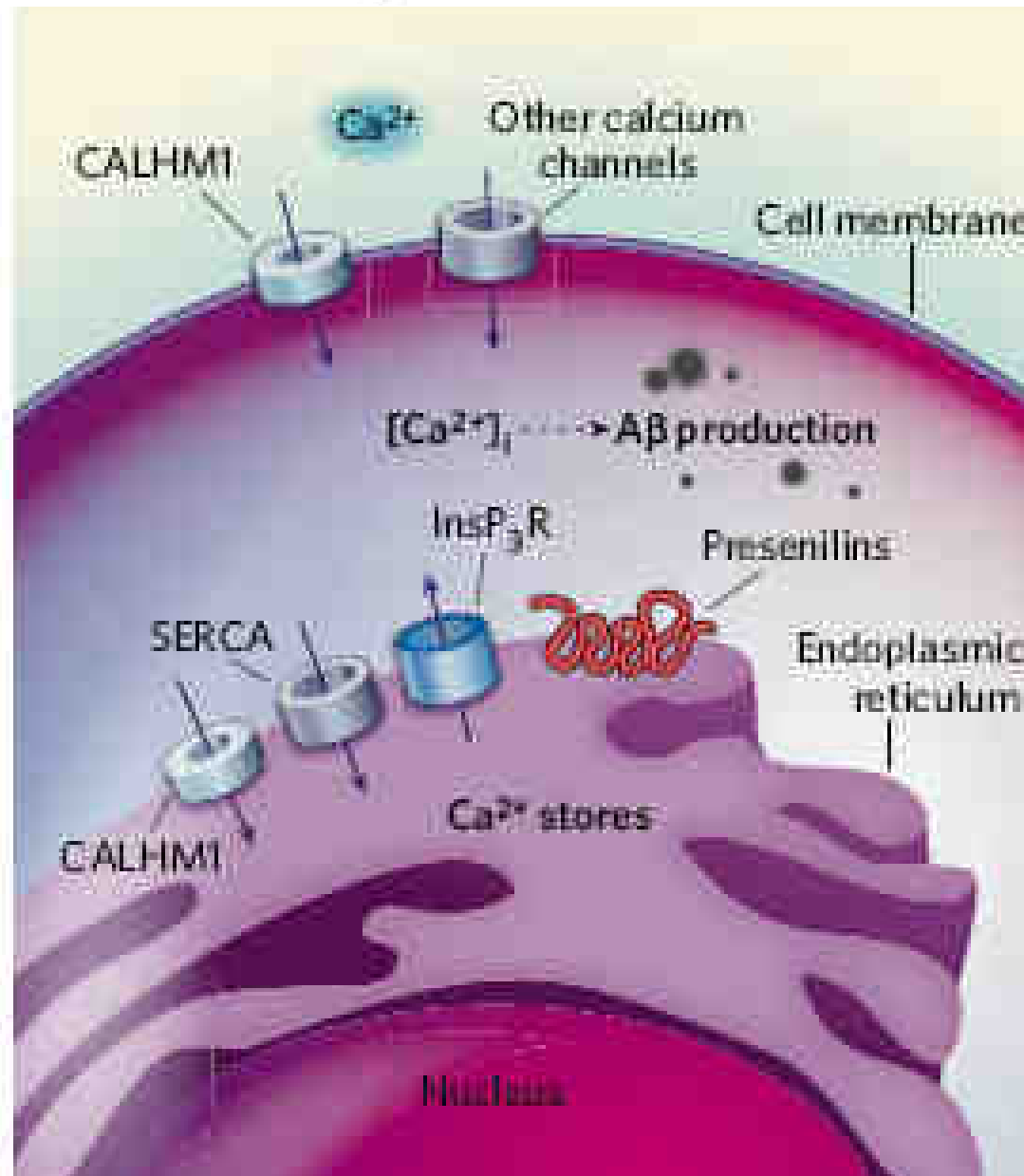


Bertram y Tanzi. *J. Clin. Invest.* 115:1449-1457 (2005).

Genes asociados con la enfermedad de Alzheimer



The latest suspect



A high-density whole-genome association study reveals that APOE is the major susceptibility gene for sporadic late-onset Alzheimer's disease.

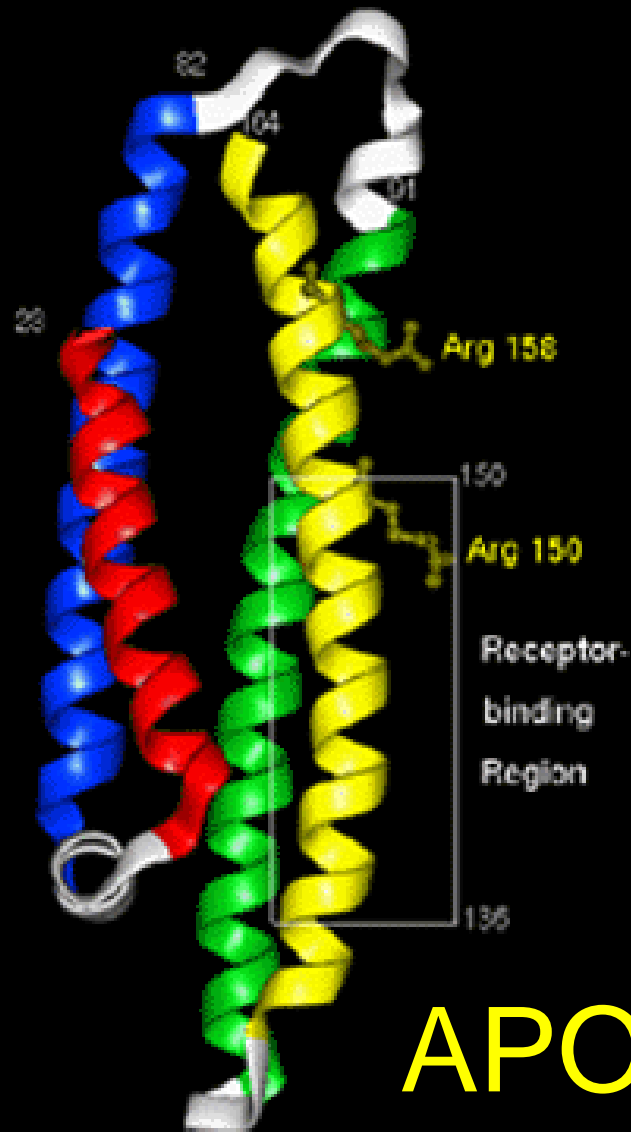
[Myers AJ](#), [Craig DW](#), [Webster JA](#), [Pearson JV](#), [Lince DH](#), [Zismann VL](#), [Beach TG](#), [Leung D](#), [Bryden L](#), [Halperin RF](#), [Marlowe L](#), [Kaleem M](#), [Walker DG](#), [Ravid R](#), [Heward CB](#), [Rogers J](#), [Papassotiropoulos A](#), [Reiman EM](#), [Hardy J](#), [Stephan DA](#).

METHOD: Study using 502,627 SNPs in **1086 AD** cases (histopathologically verified) and controls.

CONCLUSION: The **APOE locus is the major** susceptibility gene for late-onset AD in the human genome, with an OR significantly greater than any other locus.

J Clin Psychiatry. 2007 Apr;68(4):613-8.

FACTOR GENÉTICO



APOE 4

Enfermedad de Alzheimer

Factores de riesgo

(Van Duijn et al. EURODEM 1994, *Genet Epidemiol* 11: 539)

Historia del paciente

- Traumatismo craneoencefálico
- Depresión
- Edad de la madre

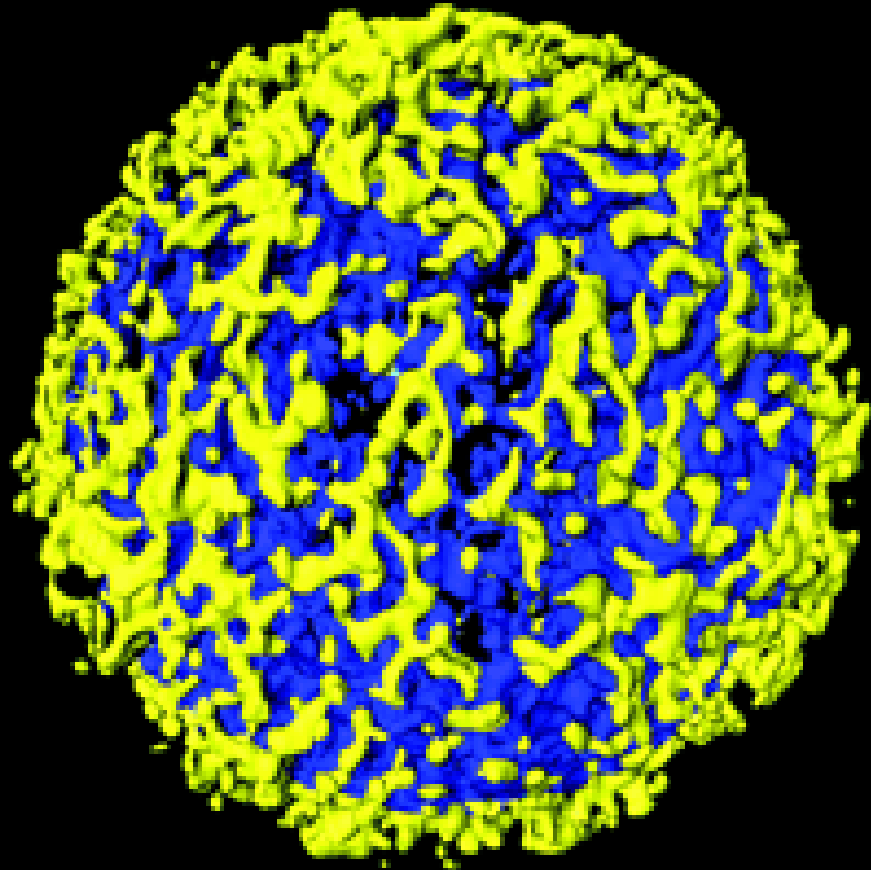


Historia familiar

- Demencia
- Síndrome de Down
- Enfermedad de Parkinson



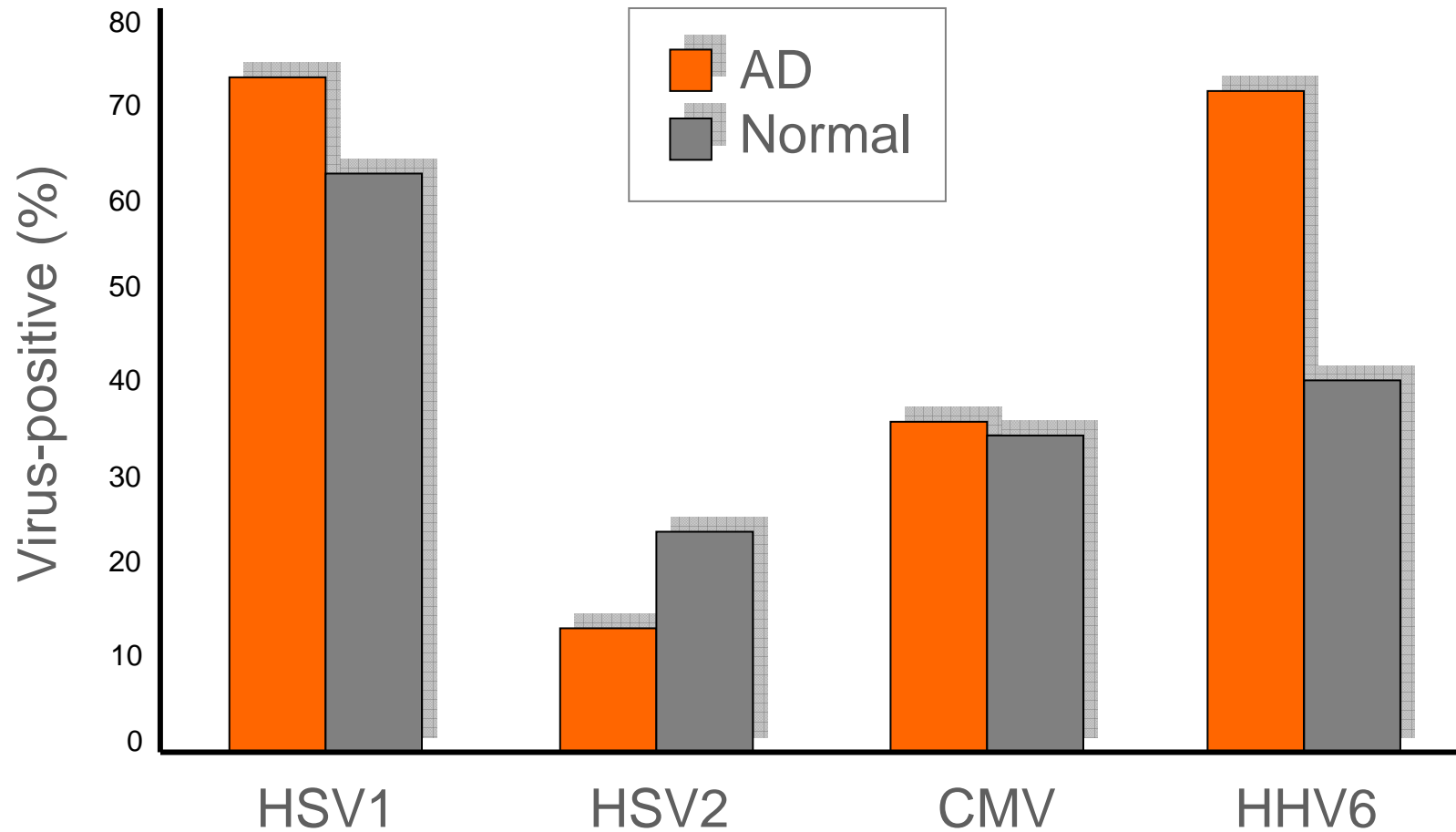
FACTOR AMBIENTAL



HERPESVIRUS

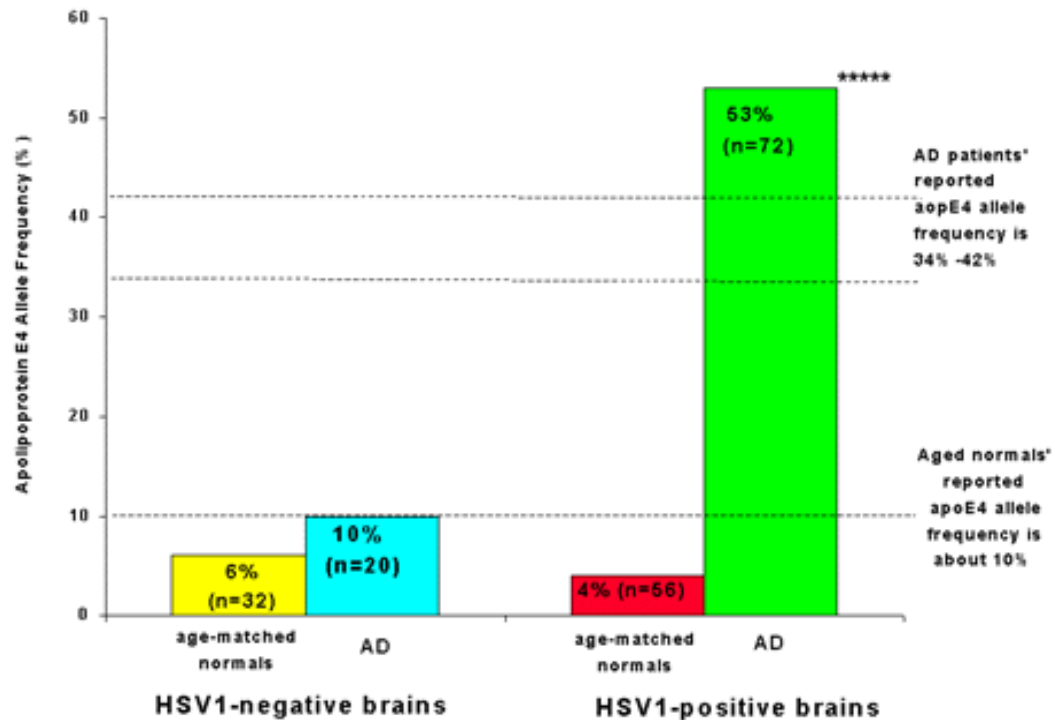
Herpesvirus en cerebro

(Woan-Ru et al. 2002, J Pathol 197:395)



Herpes simplex virus type 1 in brain and risk of Alzheimer's disease

Ruth F Itzhaki, Woan-Ru Lin, Dazhuang Shang, Gordon K Wilcock, Brian Faragher, Gordon A Jamieson



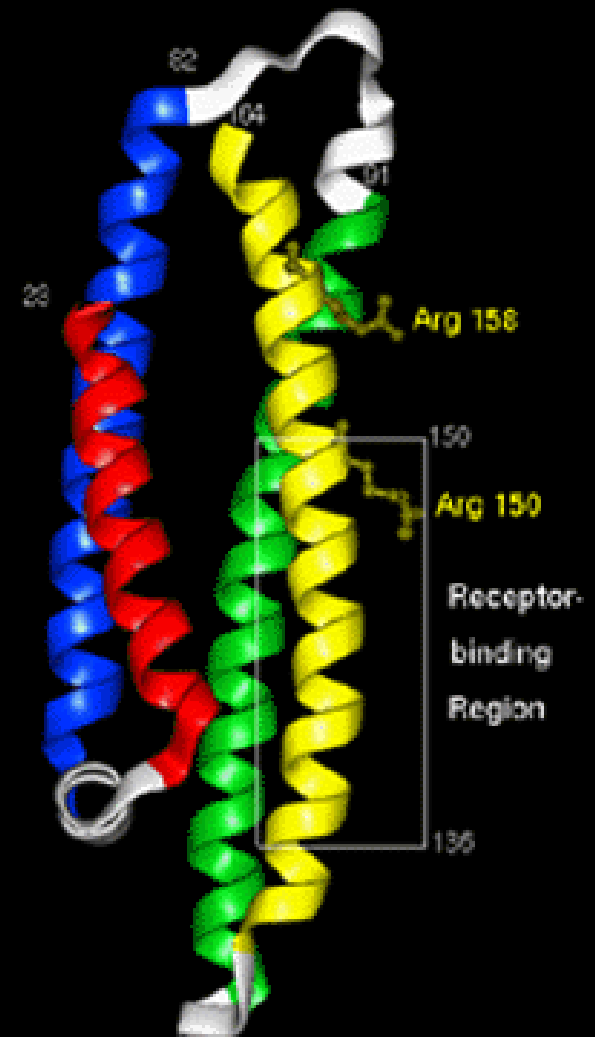
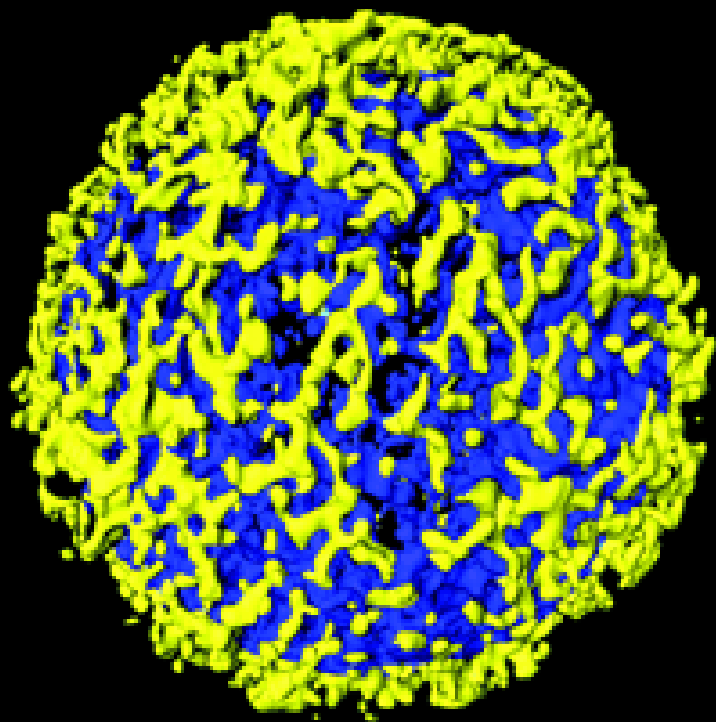
Lancet 1997; **349**: 241-44



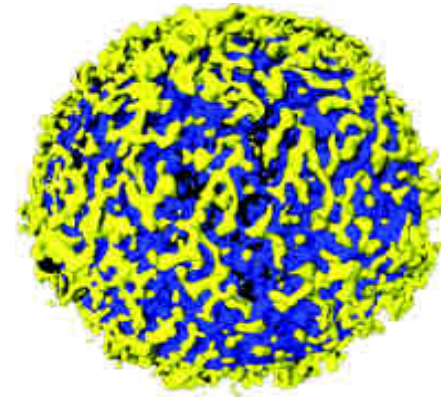
Hospital Universitario La Paz

Comunidad de Madrid

Virus y genes en la enfermedad de Alzheimer



ESTRATEGIA EXPERIMENTAL





Edad

(Nussbaum & Ellis. *N Engl J Med* 2003)

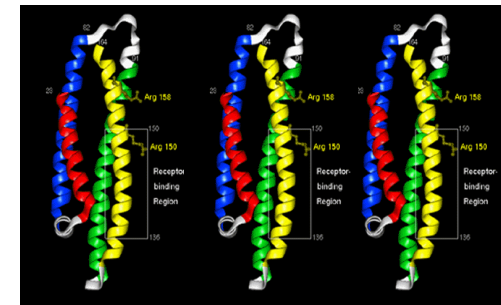


Género



APOE4

(Corder et al. *Science* 1993)



Dosis de APOE

(Bullido et al. *Nat Genet* 1998)



Factor transmisible no-genético

(Daw et al. *Am J Hum Genet* 2000)



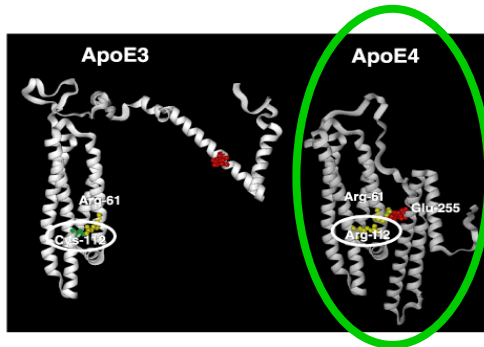
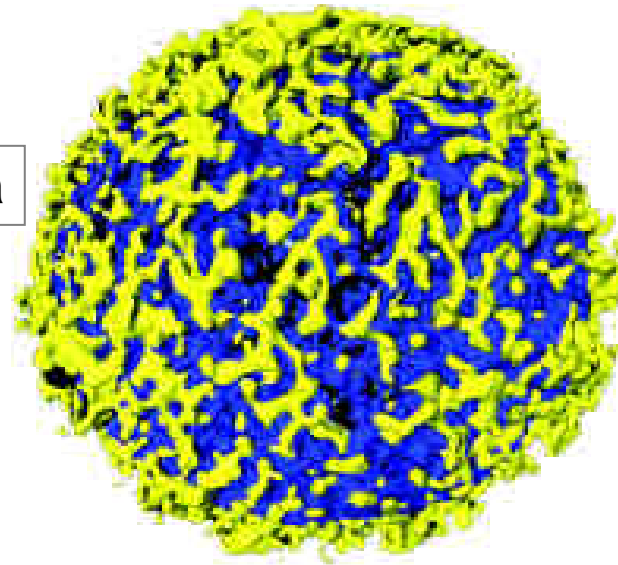
Edad

Burgos et al. J Virol 2006a



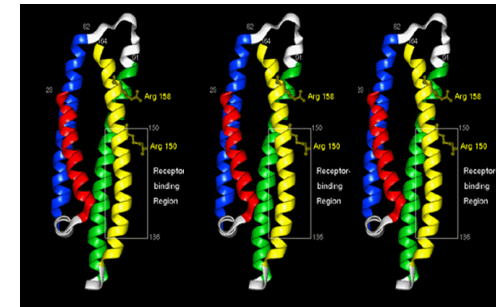
Género

Burgos et al. J Virol 2005



APOE4

Burgos et al. NeuroReport 2003
Burgos et al. J Virol 2006b



Dosis de APOE

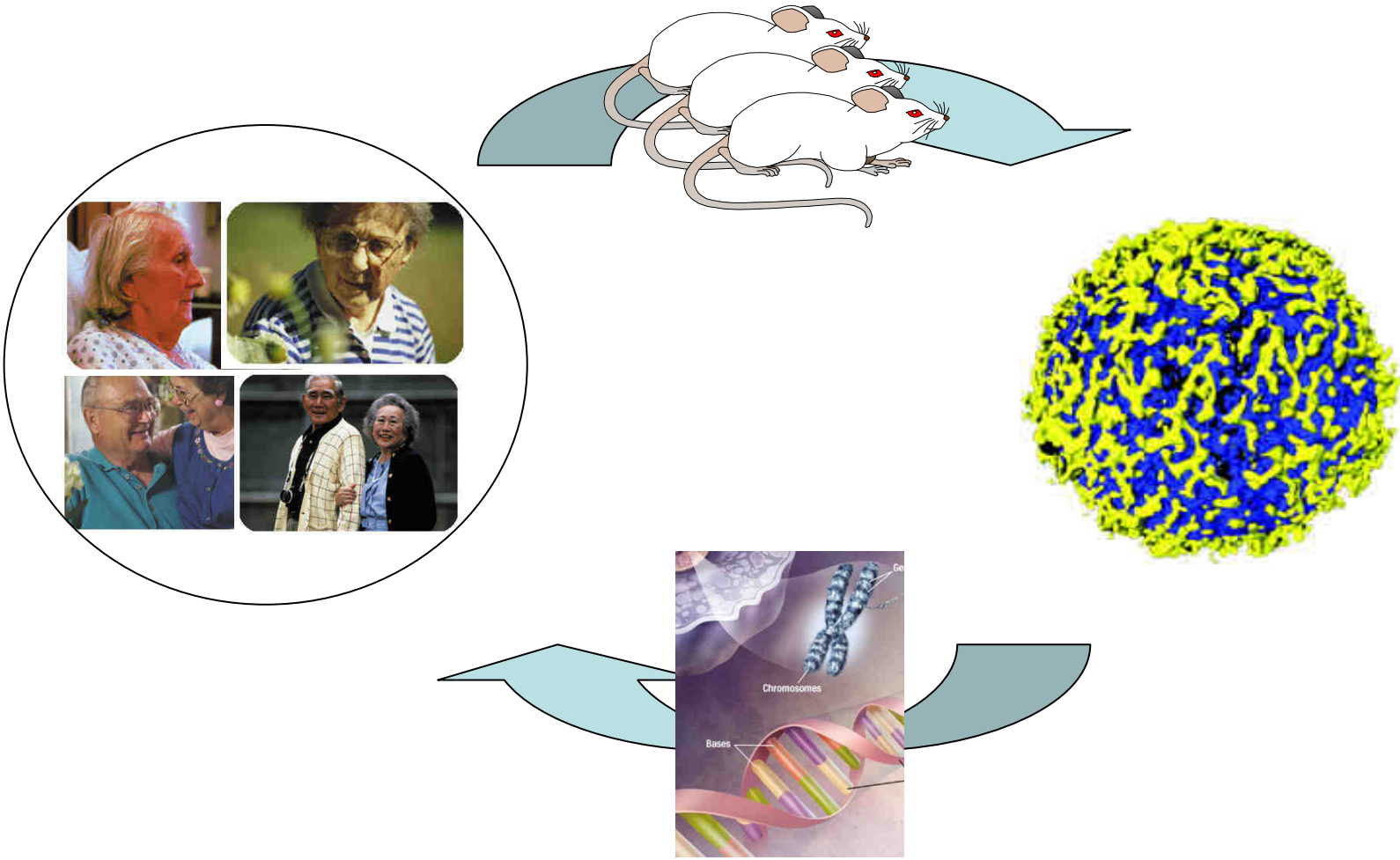
Burgos et al. J Virol 2002
Burgos et al. J Virol 2006b



Factor transmisible no-genético

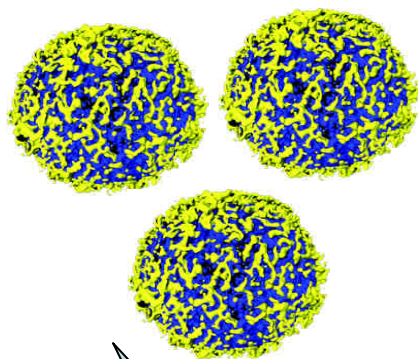
Burgos et al. J Virol 2006a

ESTRATEGIA EXPERIMENTAL

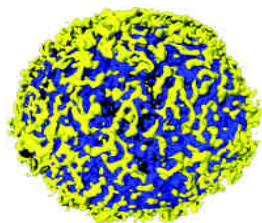


Burgos et al. *J Virol* 2002
Burgos et al. *NR* 2003

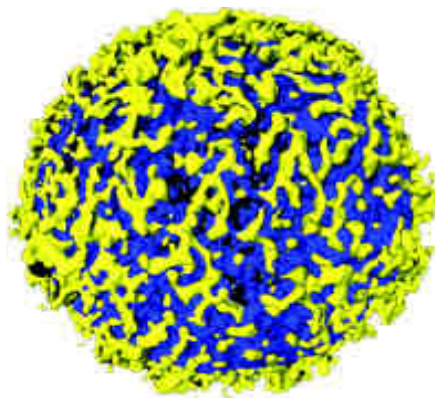
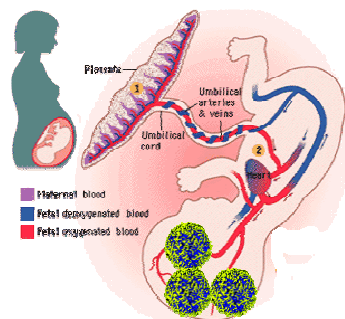
NEUROINVASIÓN
APOE



INMUNOEVASIÓN
TAP

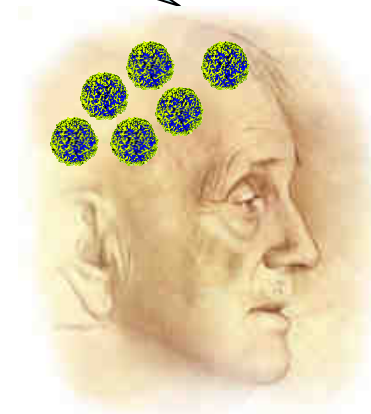


Hill et al. *Nature* 1995

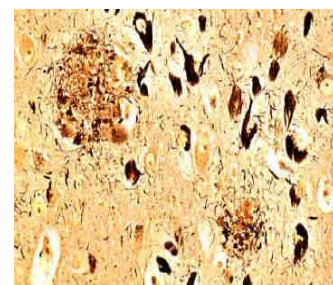


Smith et al. *Virology* 1992

REACTIVACIÓN
cAMP



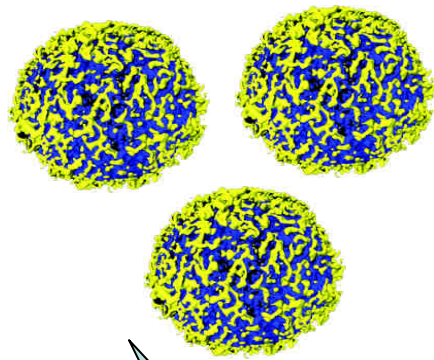
NEURODEGENERACIÓN
PKR



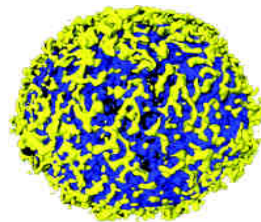
Chou et al. *Proc Natl Acad Sci USA* 1995

Corder et al. Science 1993
Bullido et al. Nat Genet 1998

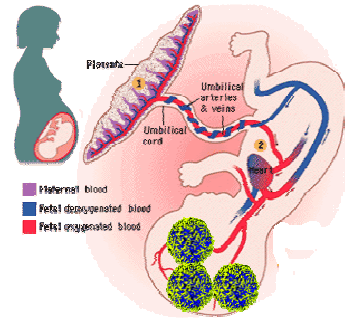
NEUROINVASIÓN
APOE



INMUNOEVASIÓN
TAP

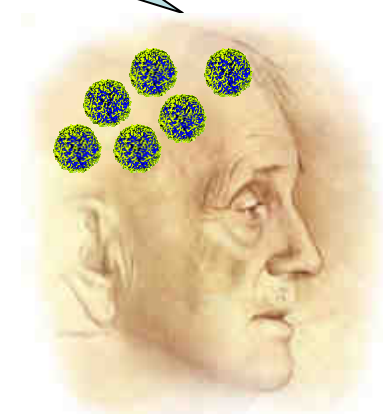


Bullido et al. Neurobiol Aging 2007

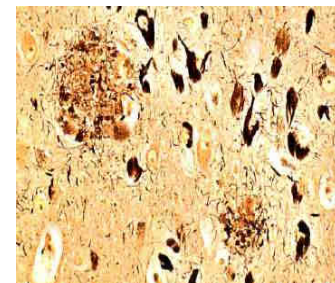


Bullido et al. Neurobiol Aging 2004

REACTIVACIÓN
cAMP



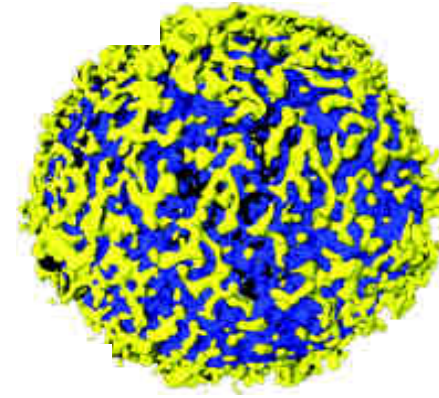
NEURODEGENERACIÓN
PKR



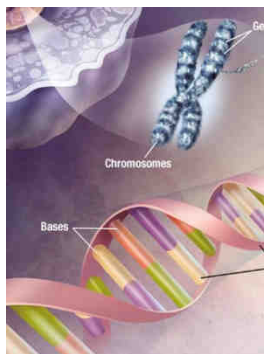
Bullido et al. Neurobiol Aging 2008

La estrategia permite ver que

Factores de riesgo de Alzheimer **favorecen la infección** por herpesvirus, en un modelo: APOE, edad avanzada, sexo femenino, transmisión materna. Burgos et al. J Virol 2002, 2005, 2006a,2006b



Genes importantes en la infección de herpesvirus modifican el riesgo de Alzheimer: APOE, TAP2, ADRB1/GNB3. Bullido et al. Nat Genet 1998; Neurobiol. Aging 2004, 2007, 2008



Patogénesis de Alzheimer?

Mutaciones en APP, PS-1 o PS-2

Oxidative damage is the earliest event in Alzheimer disease. Nunomura et al., J Neuropathol Exp Neurol 2001; 60:759.

HSV-1

Herpes simplex virus type 1 latency in the murine nervous system is associated with oxidative damage to neurons. Valvi-Nagy et al., Virology 2000; 278:309-21.

Daño Oxidativo

Tangles

Evolution of neuronal changes in the course of Alzheimer's disease. Braak H. & Braak E., J Neural Transm Suppl 1998; 53:127.

Muerte neuronas

Abeta production as consequence of cellular death of a human neuroblastoma overexpressing APP. Recuero et al., FEBS Lett 2004; 570:114.

Amiloide

Demencia

Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database

Lars Bertram¹, Matthew B McQueen^{2,3}, Kristina Mullin¹, Deborah Blacker^{2,4} & Rudolph E Tanzi¹

(b) Sample sizes required for 80% power across different combinations of odds ratios and allele frequencies^b.

OR	Minor allele frequency in general population			
	0.05	0.10	0.20	0.50
1.10	35,924	18,962	10,636	7,046
1.15	15,990	8,962	4,830	3,208
1.25	6,148	3,286	1,912	1,268
1.50	1,798	968	540	376
1.75	884	478	278	202

El estudio de las causas de la enfermedad de Alzheimer requiere la Colaboración:

Investigadores básicos

Investigadores clínicos

Asociaciones de familiares

- Proyecto BNADN: Muestras de ADN de pacientes con enfermedad de Alzheimer y otras enfermedades neurológicas.



Genoma España



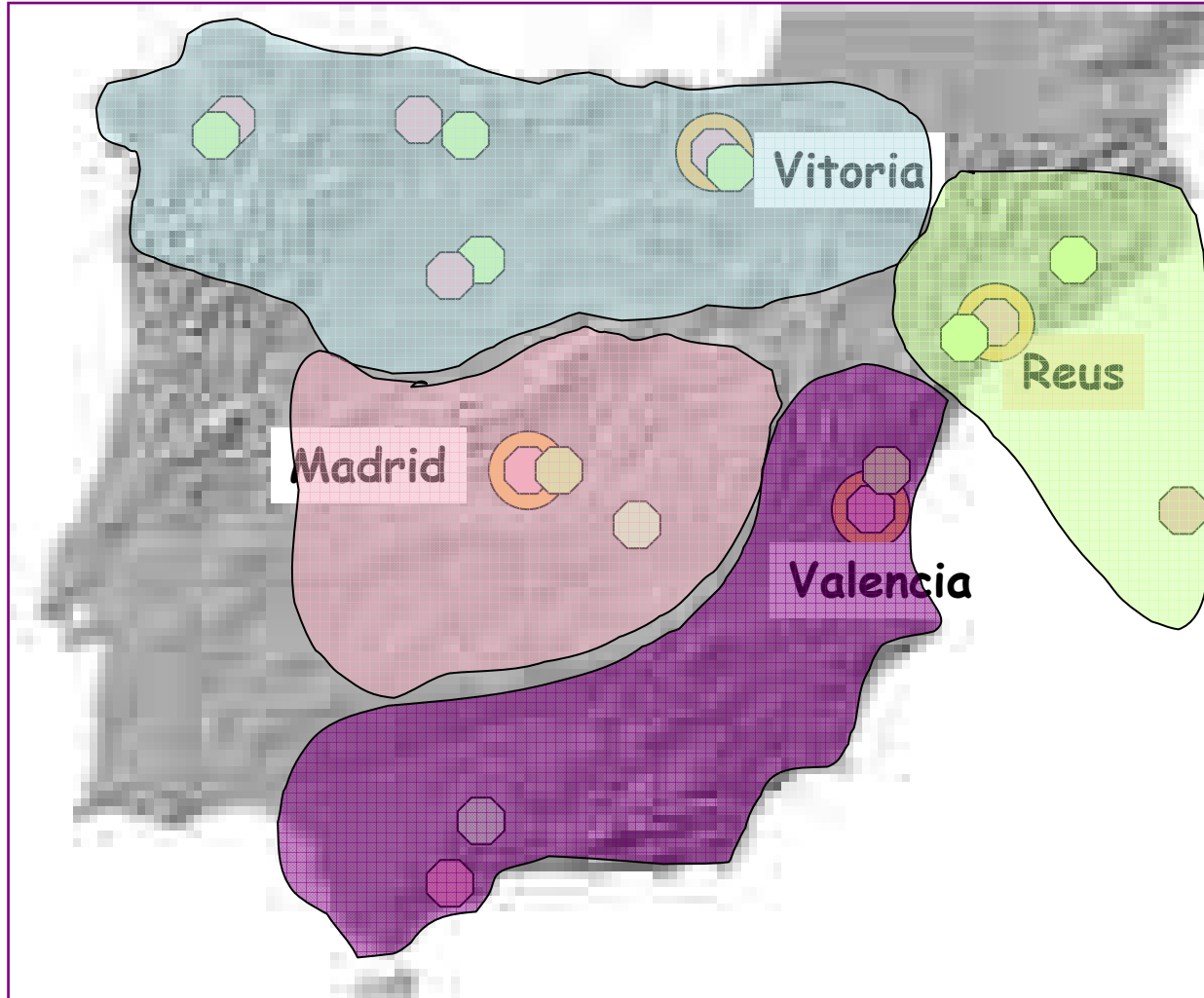
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**NODO DE ENFERMEDADES
NEUROPSIQUIÁTRICAS (NEP) DEL
BANCO NACIONAL DE ADN:**

Toledo, 15 de Diciembre de 2007



banco adn®



- Sub-nodo NEP
- ⬡ Centro enfermedades psiquiátricas
- ⬡ Centro enfermedades neurológicas
- ⬡ Futuro Centro

BioBanc IRCIS

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