

Alzheimer's Disease EB101-Vaccine



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Coruña-Madrid



Alzheimer's Disease



Memory disorders
Behavioral changes
Functional decline



Alzheimer's Disease



5th Cause of Death
Prevalence:

60-65: 1%

80-85: 25-30%

+90: 50%



Alzheimer's Disease

Genotype

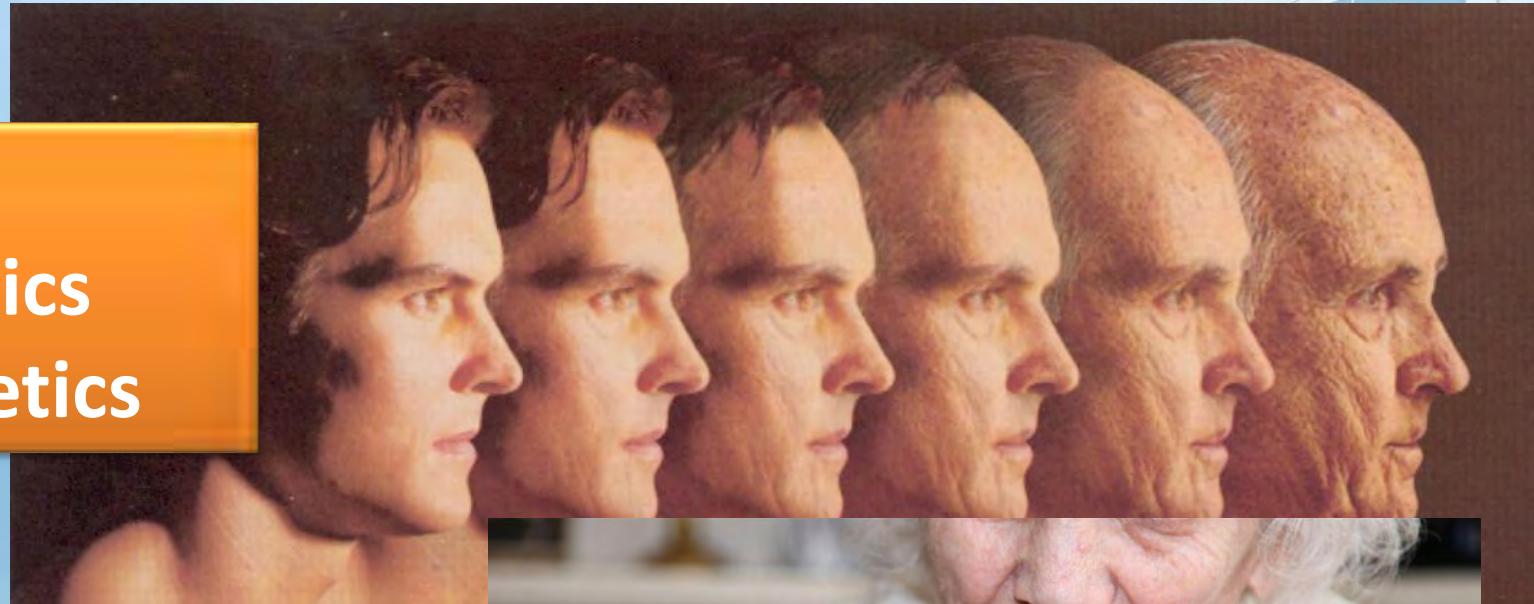
vs

Phenotype



Alzheimer's Disease

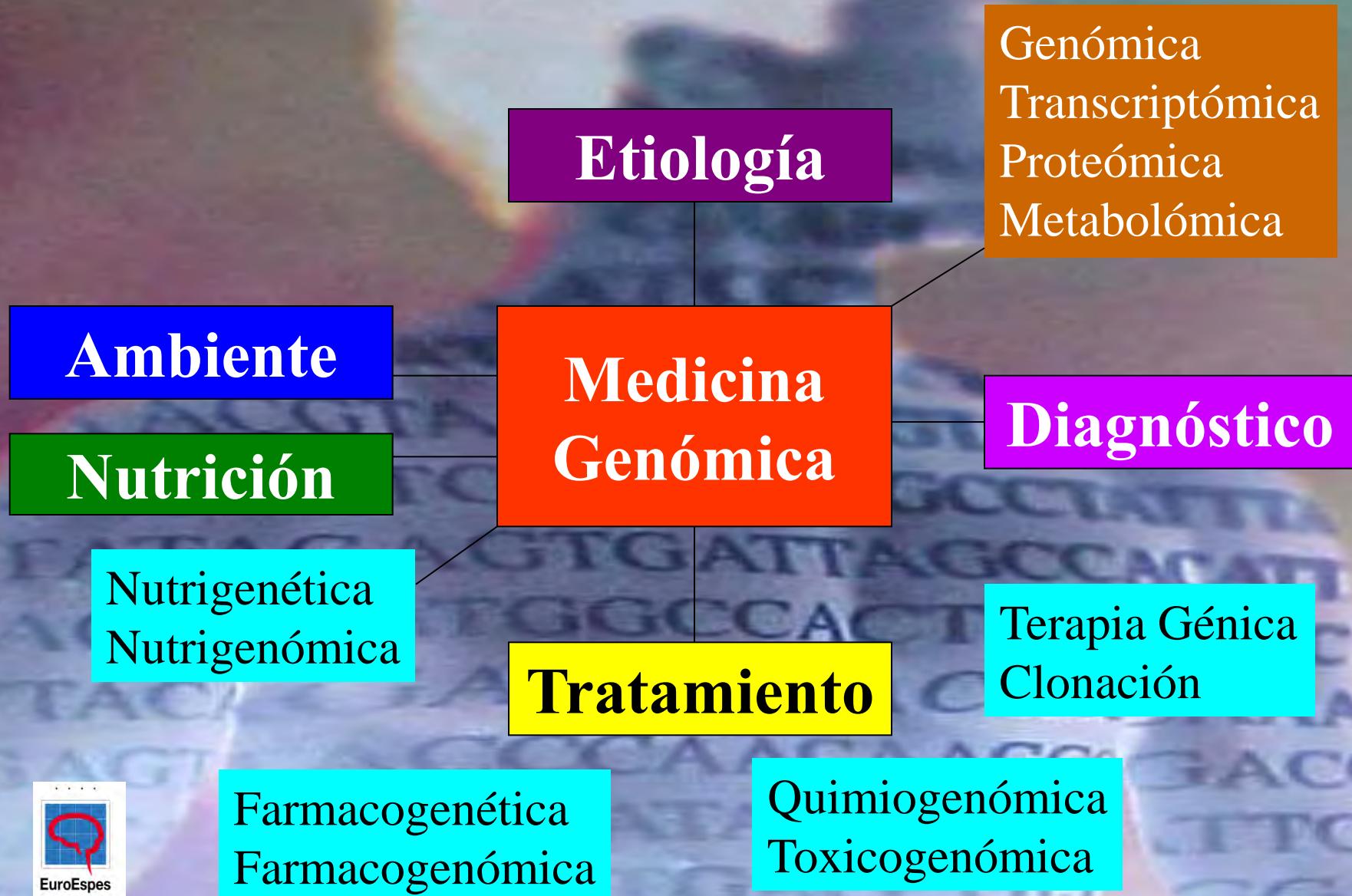
Aging
Genomics
Epigenetics

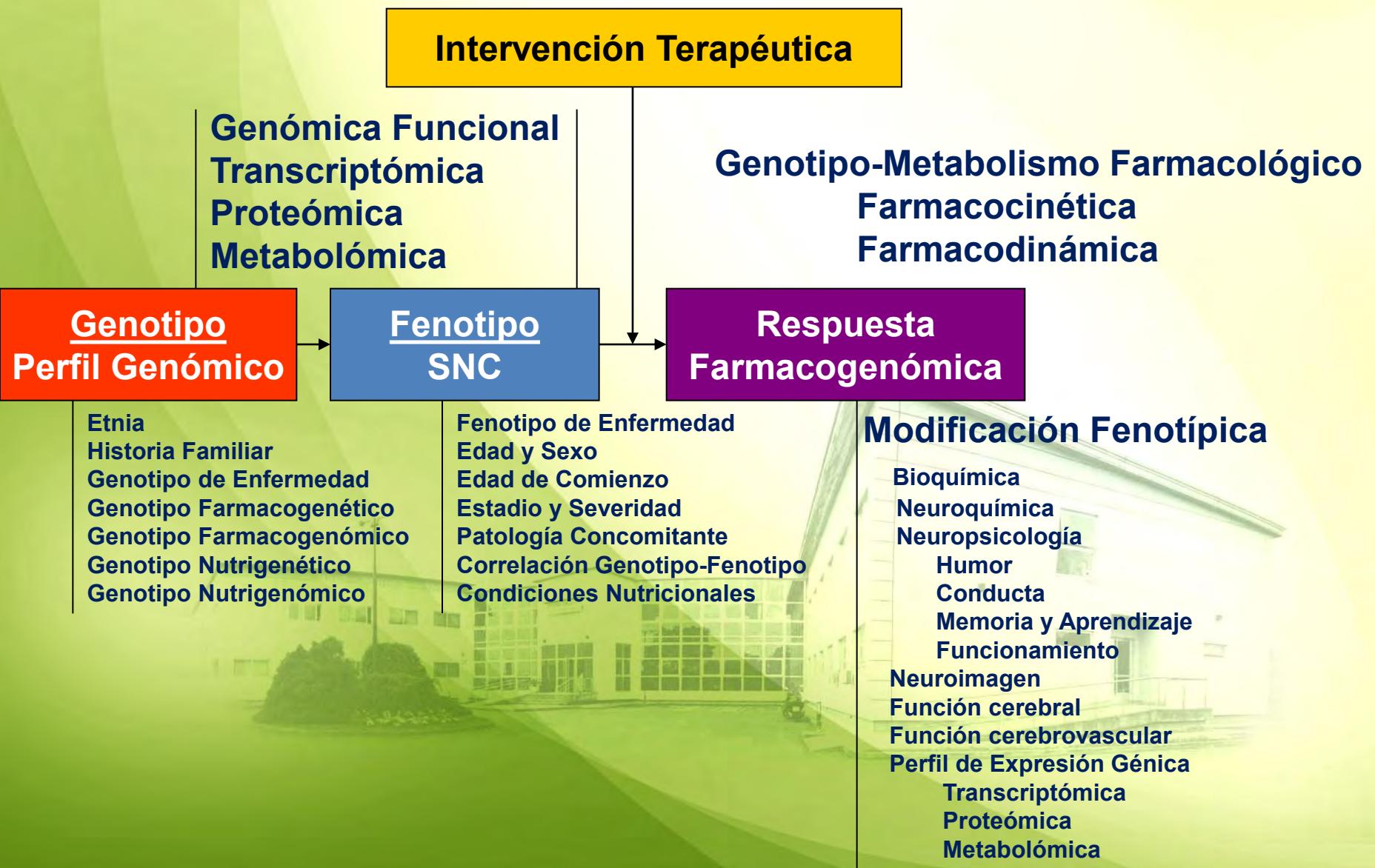


Cerebrovascular disorders
Metabolic disorders
Environmental factors



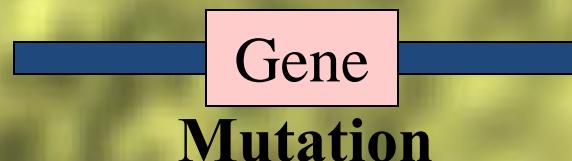
Programa EuroEspes de Medicina Genómica





Inheritance of Monogenic and Polygenic/Multifactorial/Complex disorders

Monogenic Disorder



Abnormal Protein

Inheritance Pattern

Mendelian

Dominant
Recessive
X-Linked

5-10%

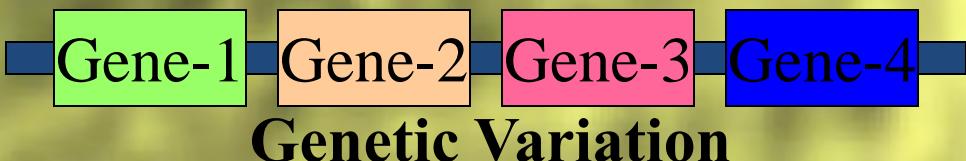
Phenotypic Expression

100% Genetic Risk in Population

Family Risk

100% Mendelian Genetics

Polygenic/Complex Disorder



Abnormal Protein Network

Inheritance Pattern

Non-Mendelian
Complex
Susceptibility

80-90%

Phenotypic Expression

Variable Genetic Risk Associated with Environmental Factors

Family Risk

Variable Depending upon Environmental Factors
and/or Associated Medical Conditions

Alzheimer's Disease

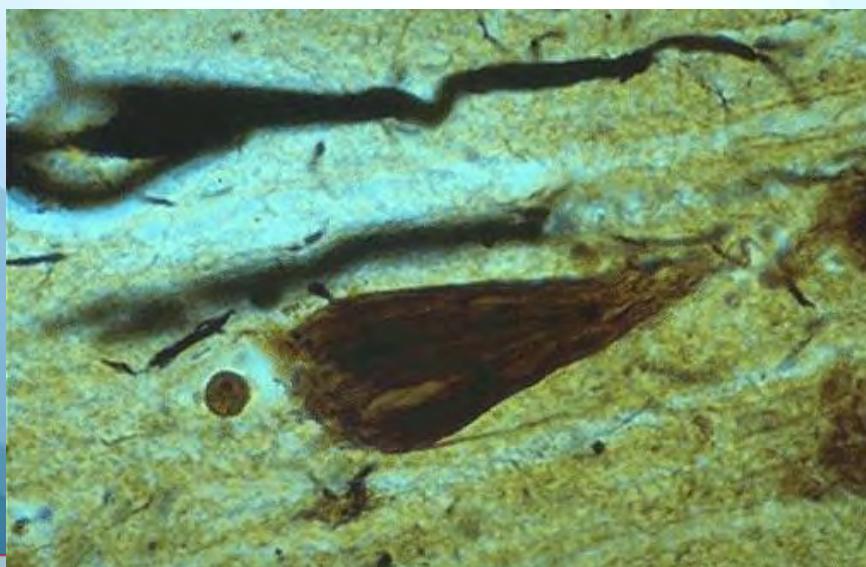
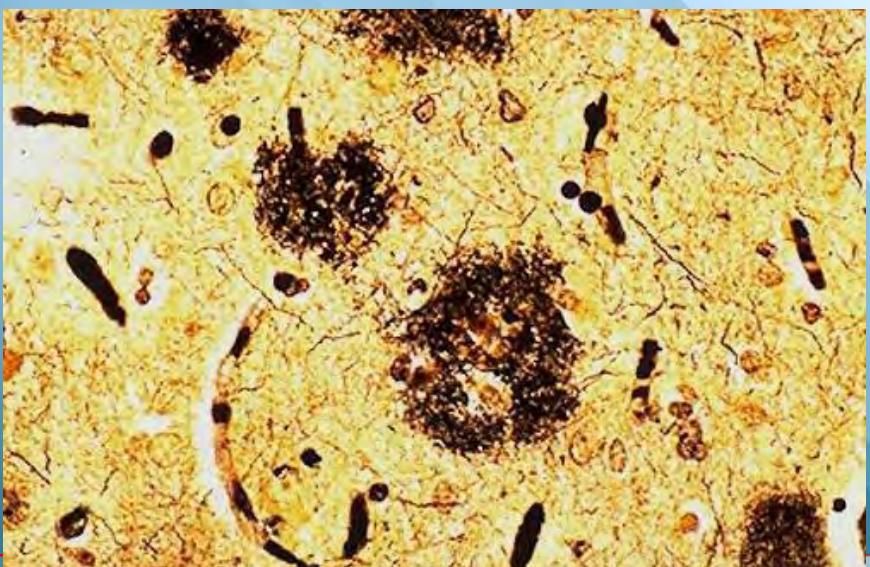
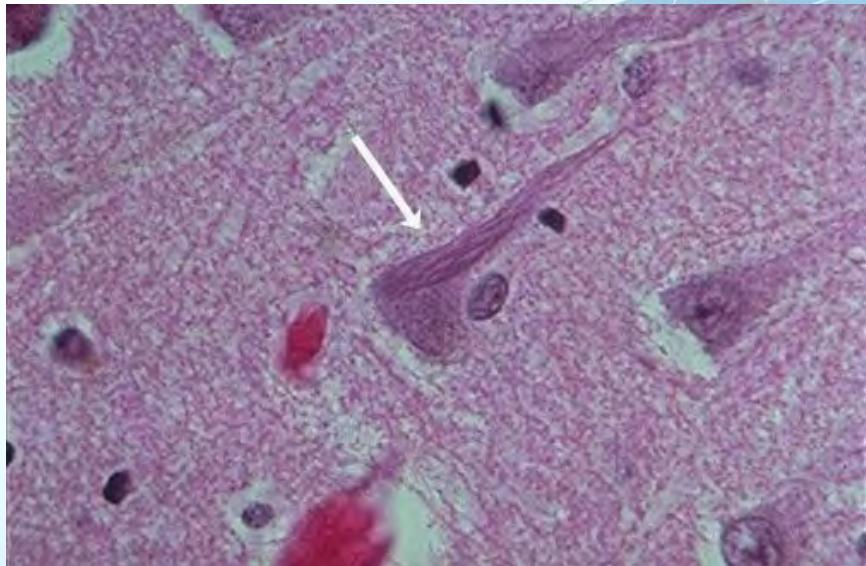
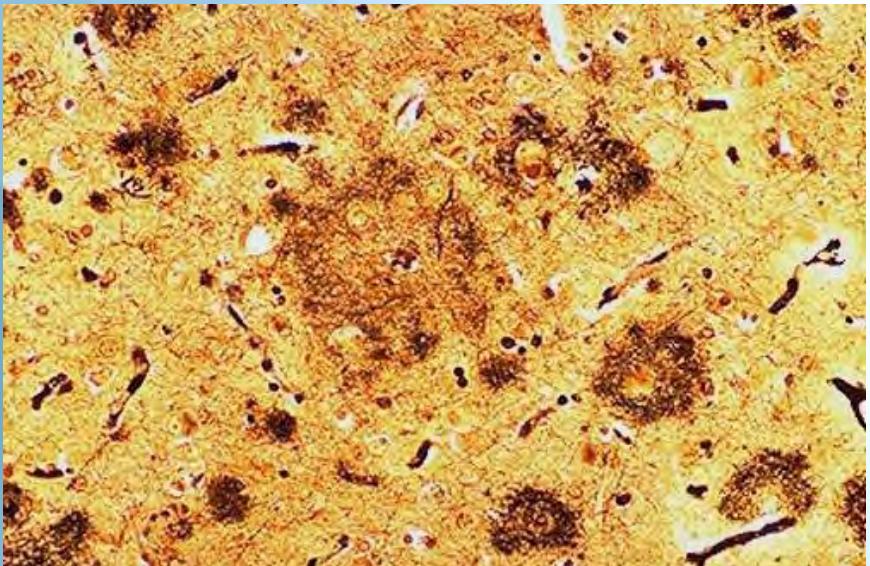
Pathogenesis



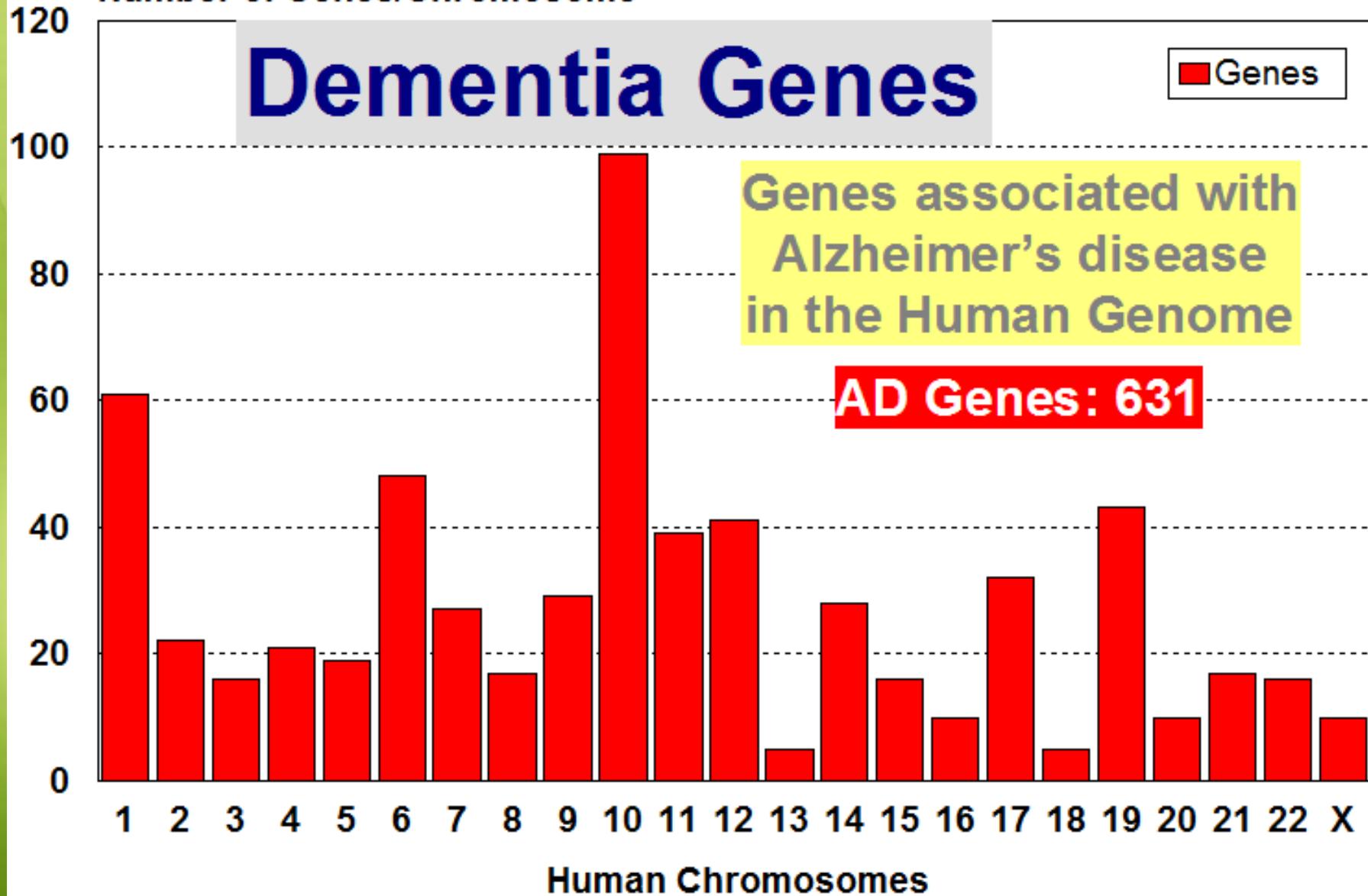
Alzheimer's Disease Macroscopic Neuropathology



Alzheimer's Disease Microscopic Neuropathology

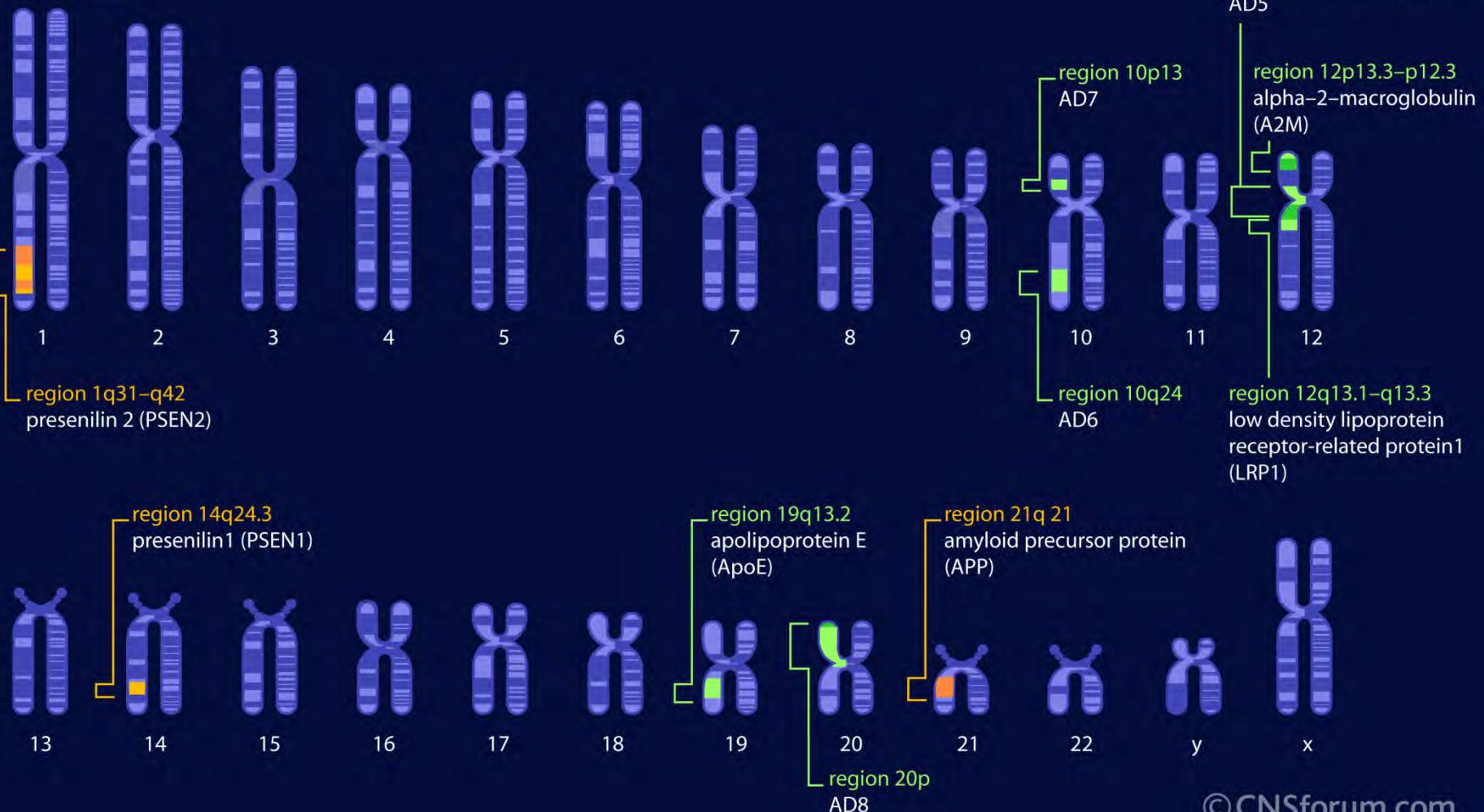


Number of Genes/Chromosome



regions implicated in Alzheimer's disease

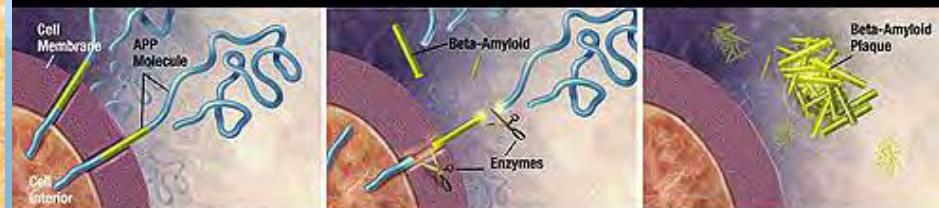
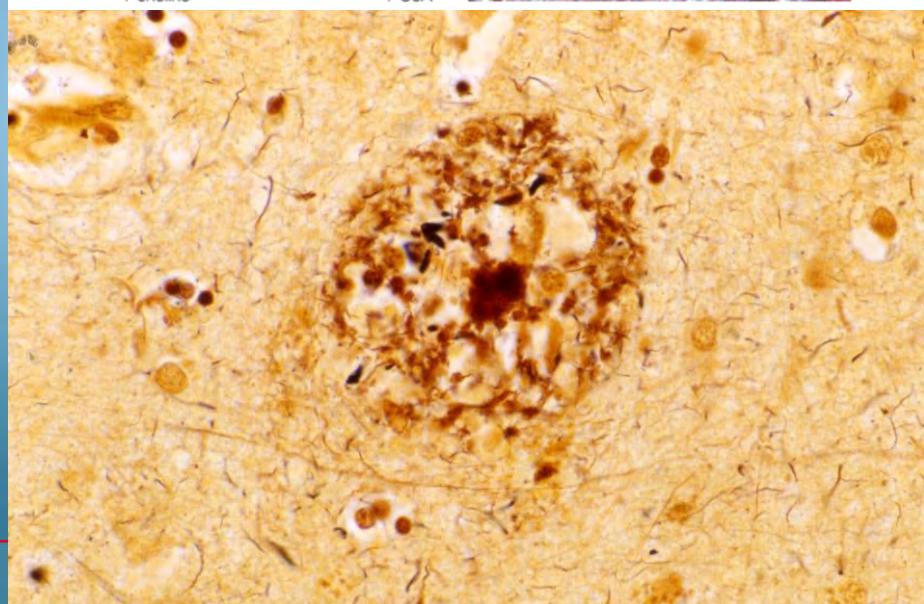
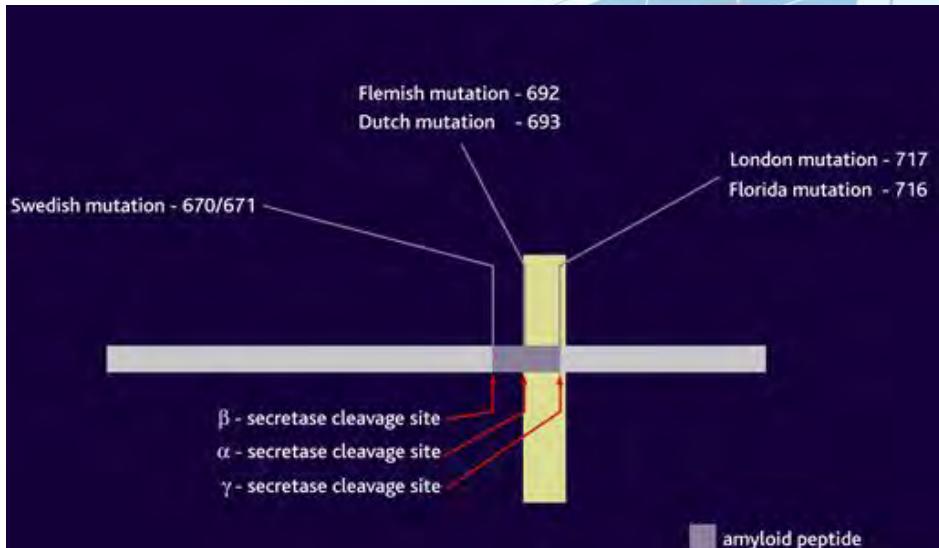
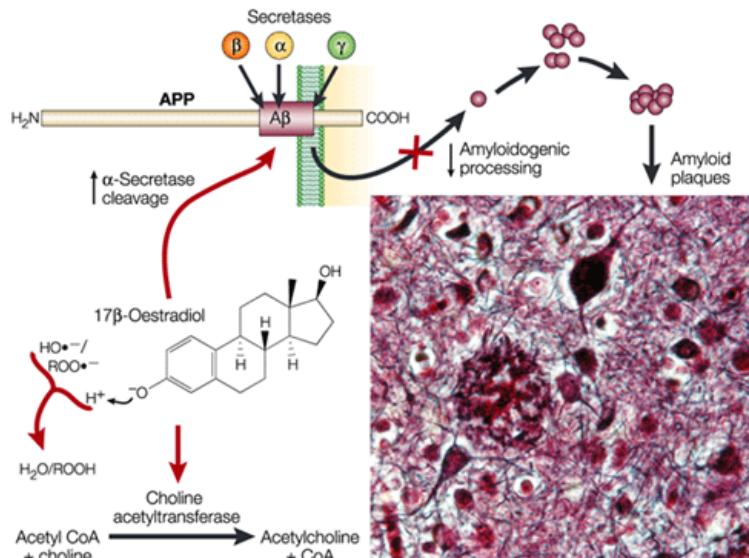
early onset
late onset



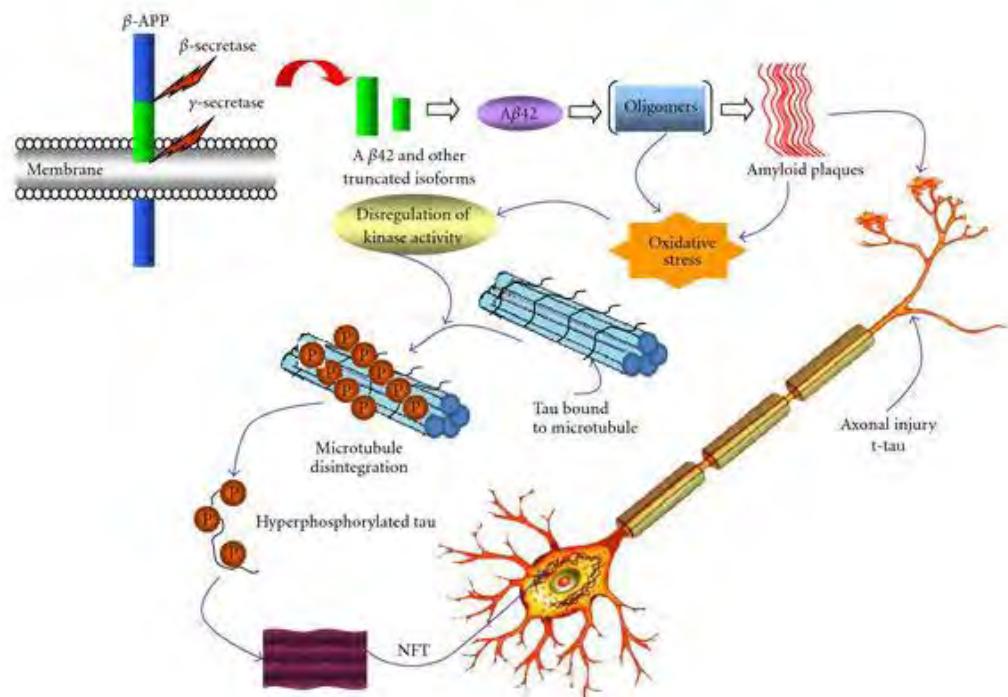
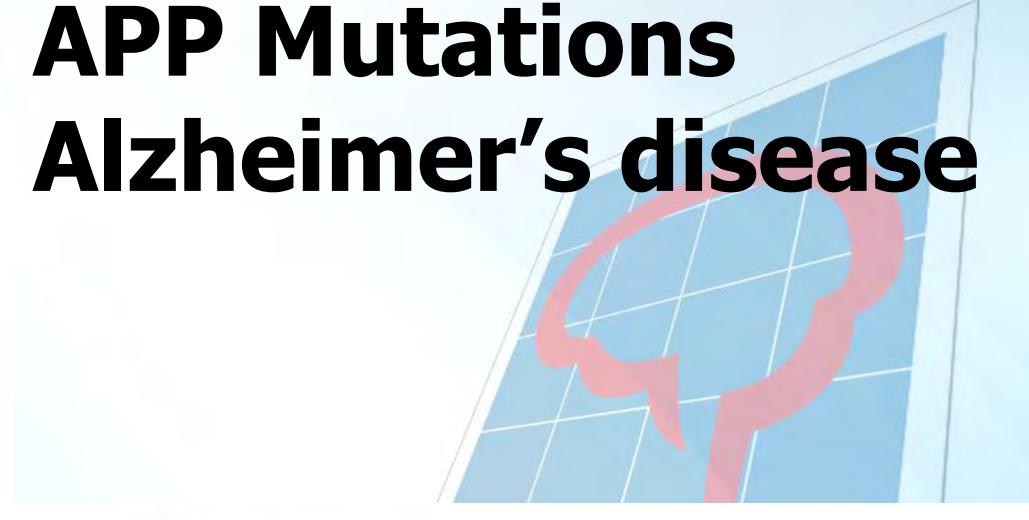
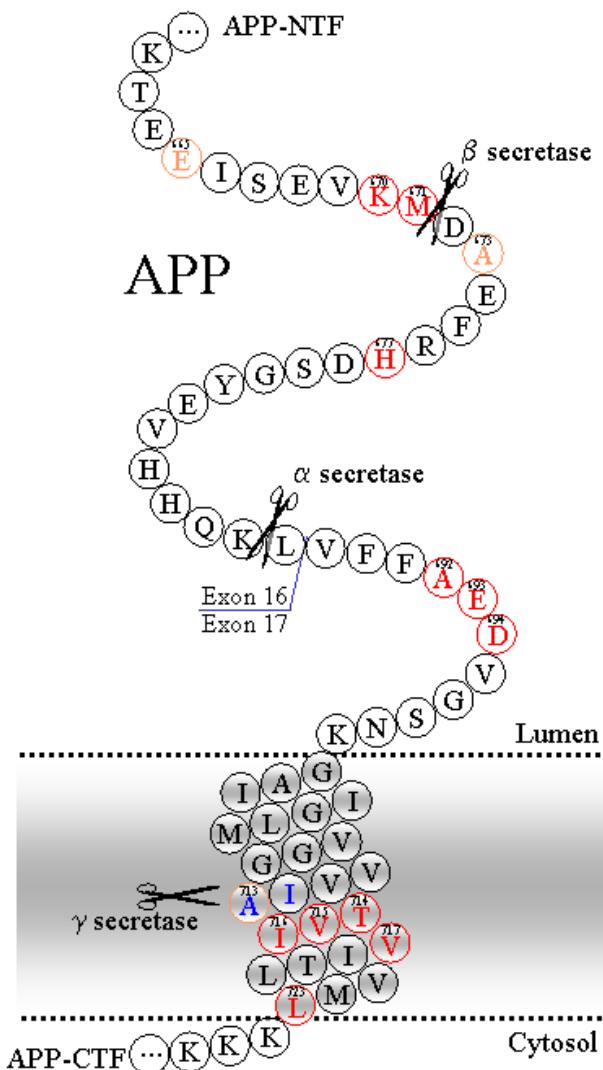
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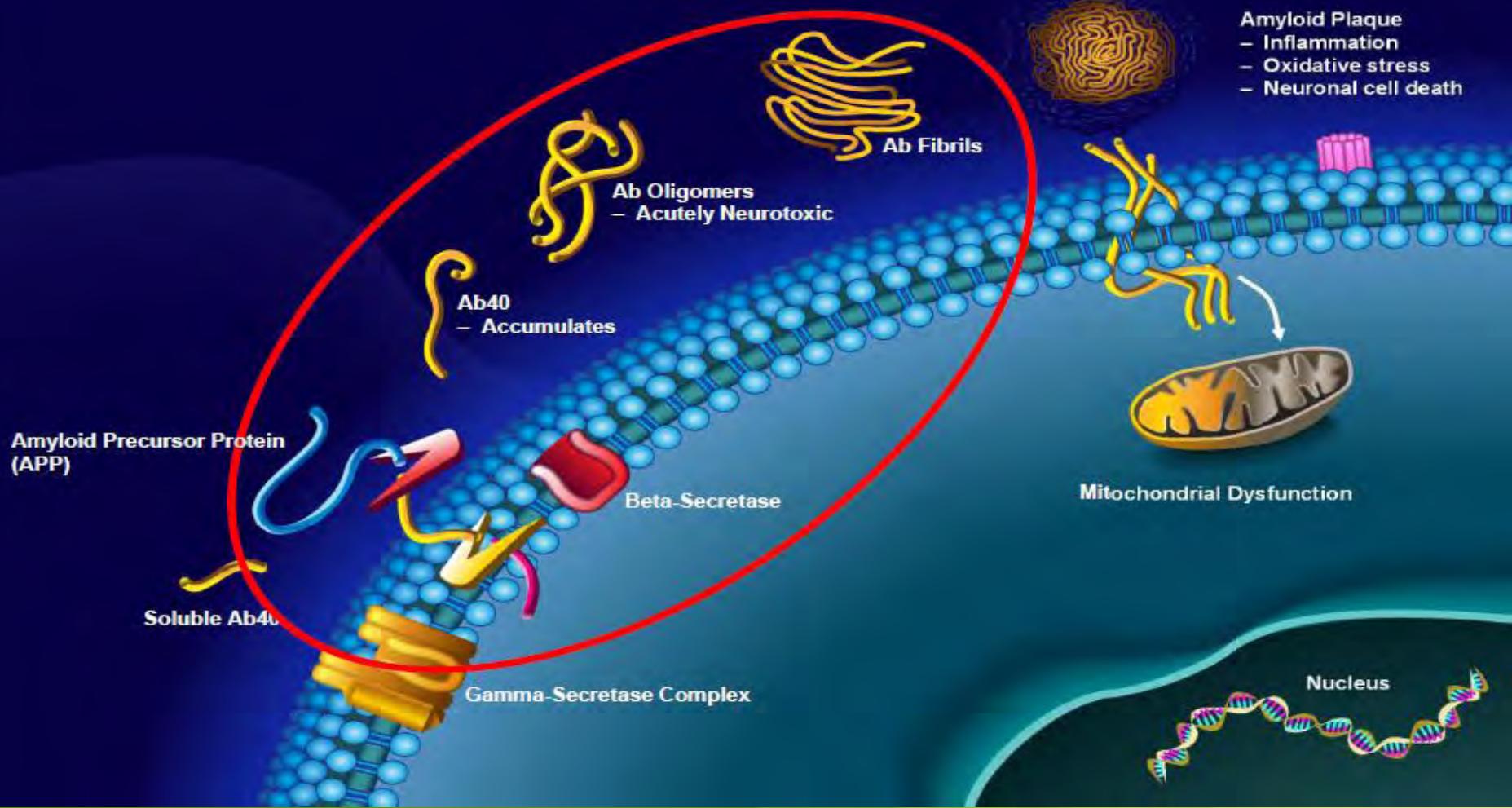
APP Mutations



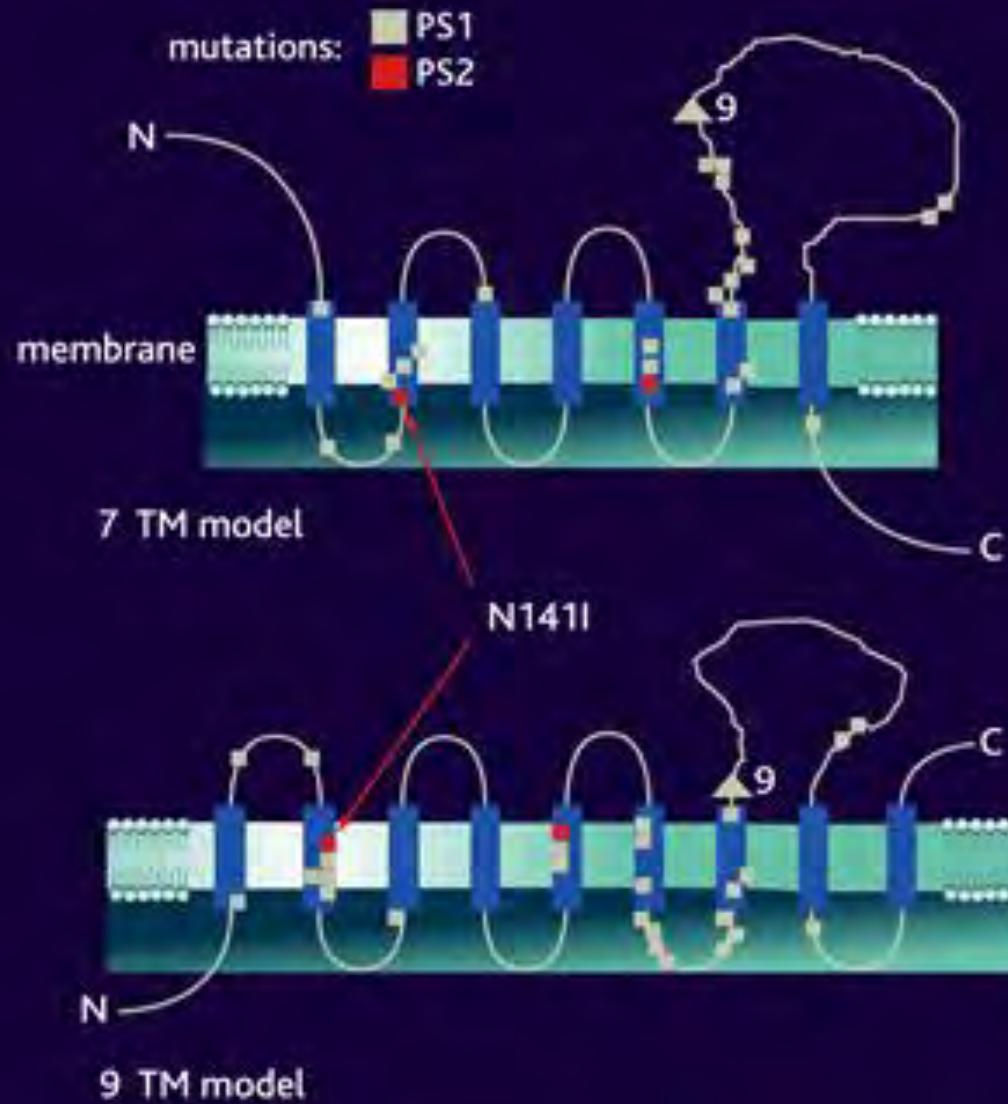
APP Mutations Alzheimer's disease



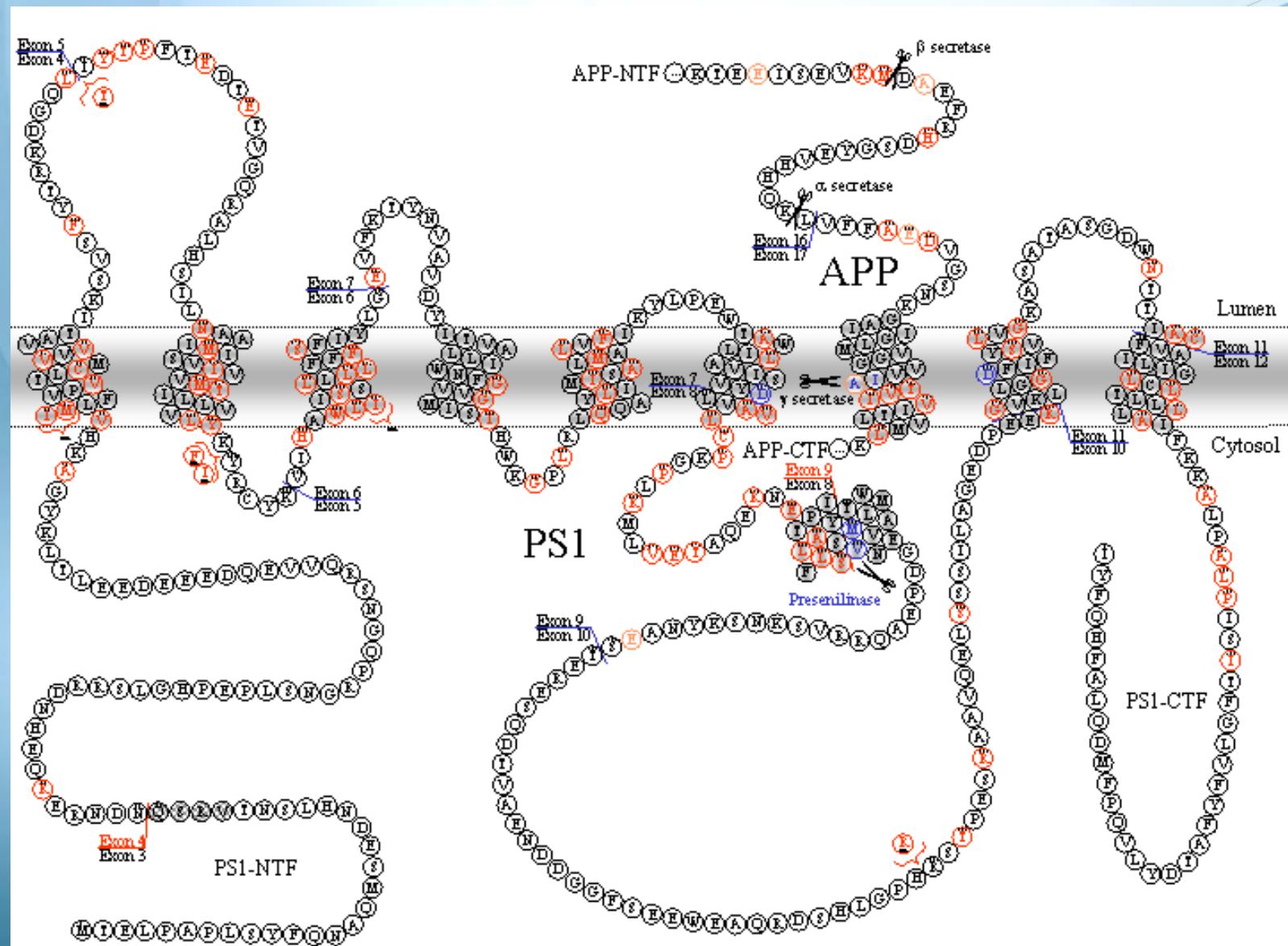
Amyloid Plaque Formation in Alzheimer's disease



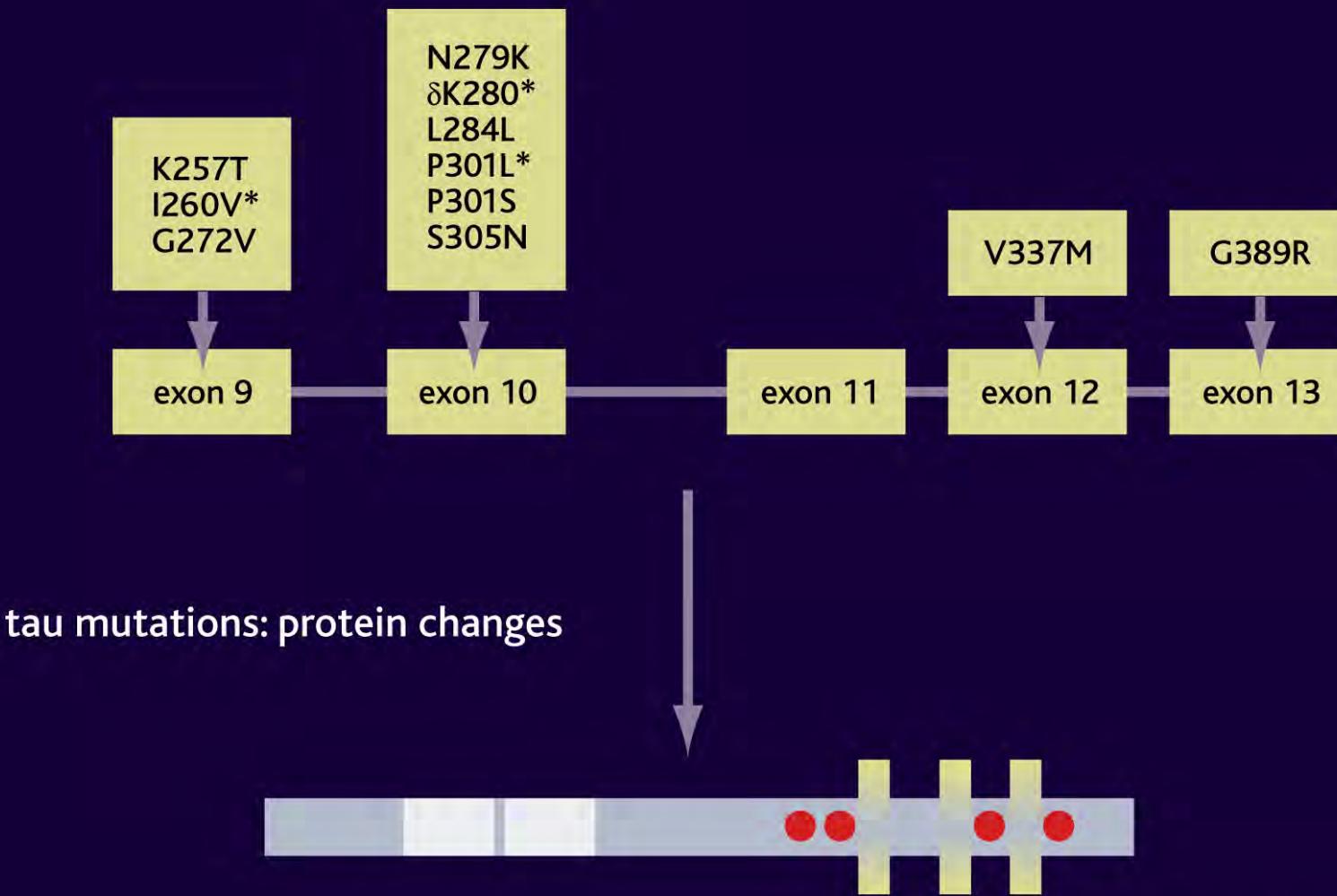
Presenilin-1 (PSEN1) and 2 (PSEN2) Mutations



Presenilin-1 (PSEN1) Mutations in Alzheimer's disease

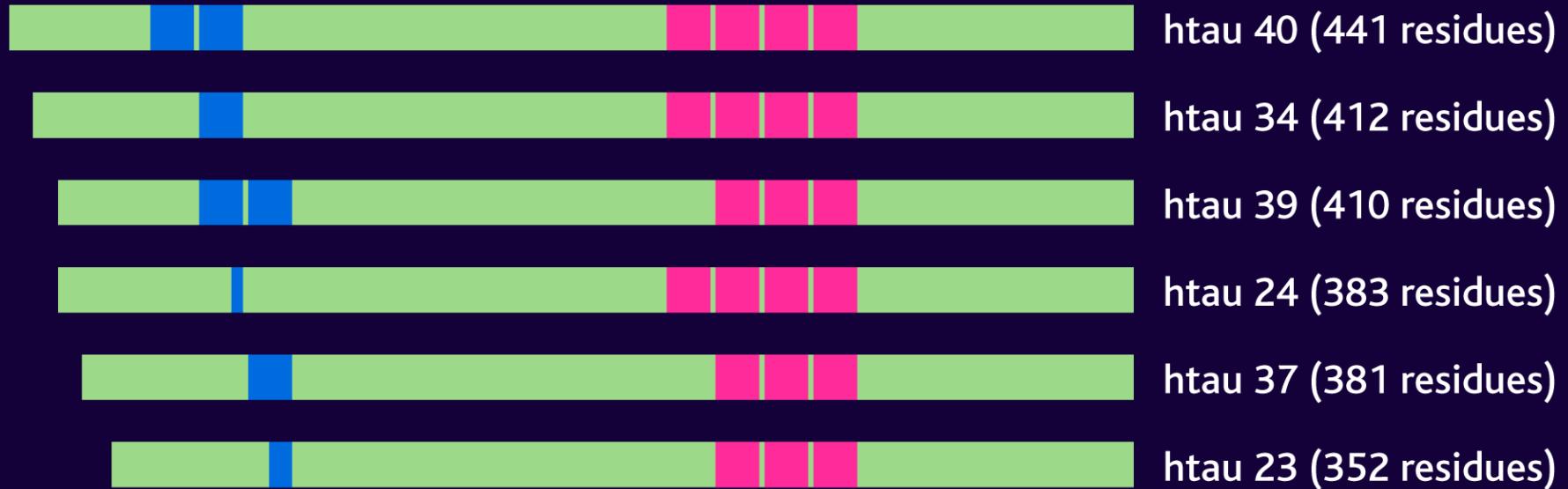


MAPT Mutations

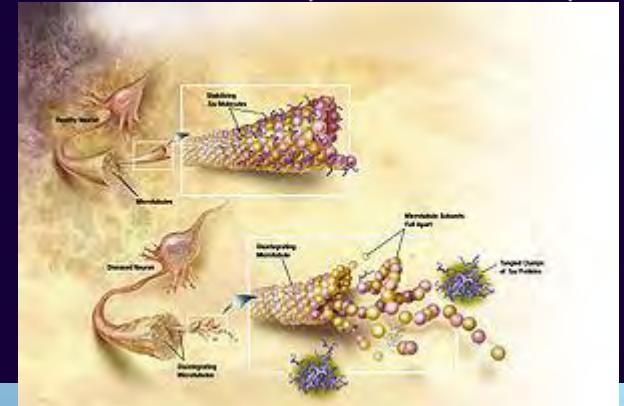


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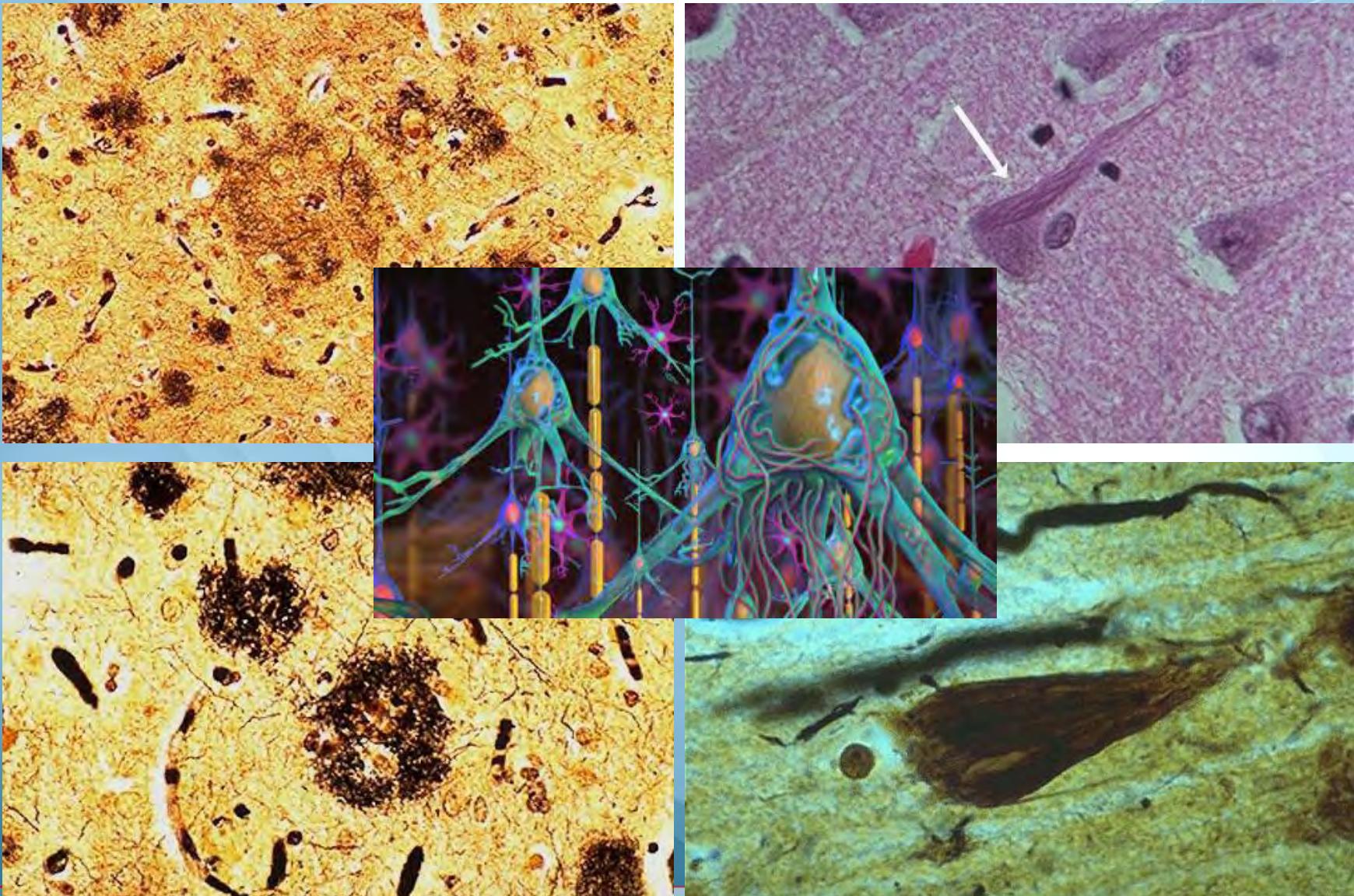




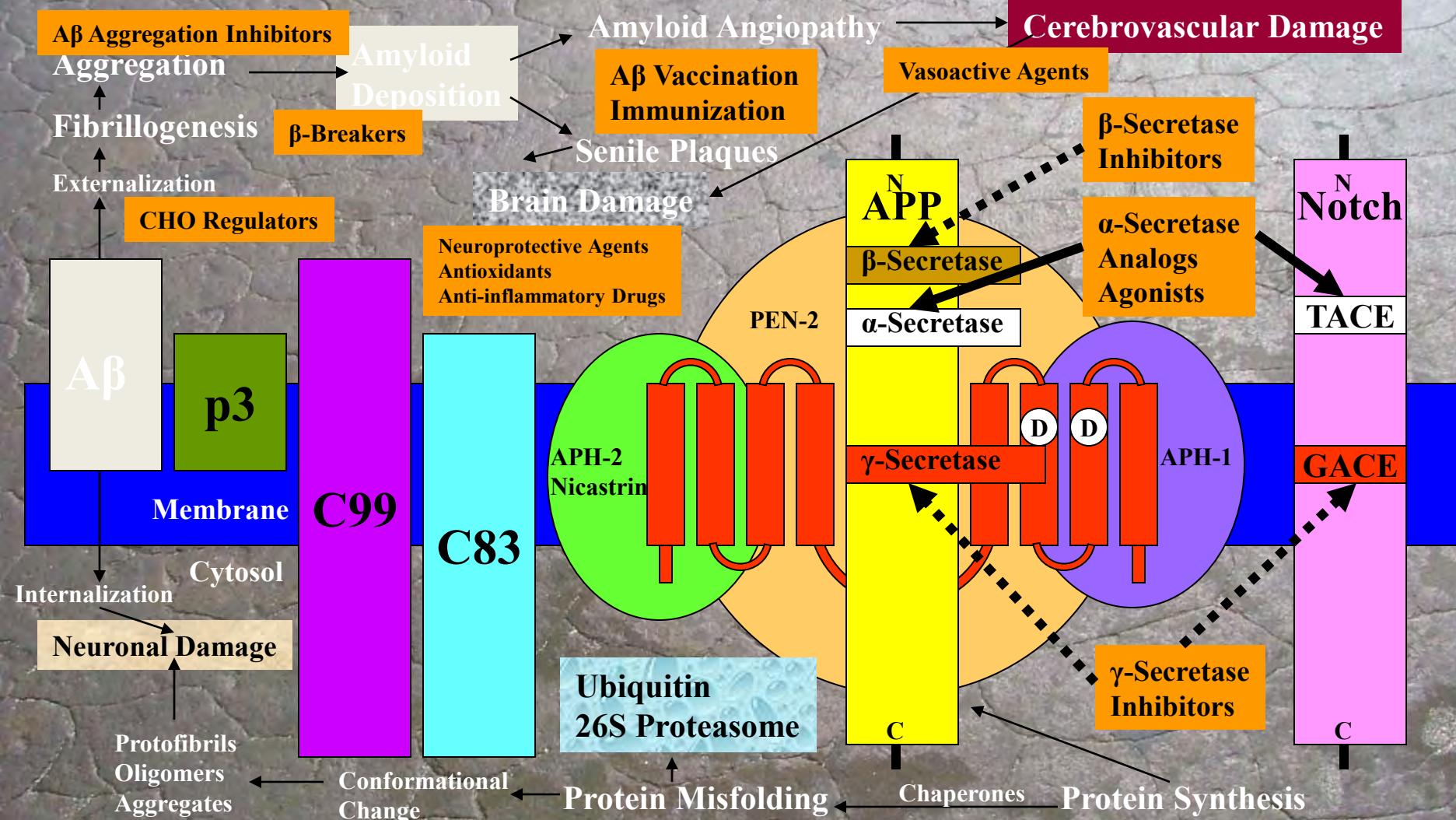
microtubule binding domains
 N-terminal inserts



Alzheimer's Disease Microscopic Neuropathology



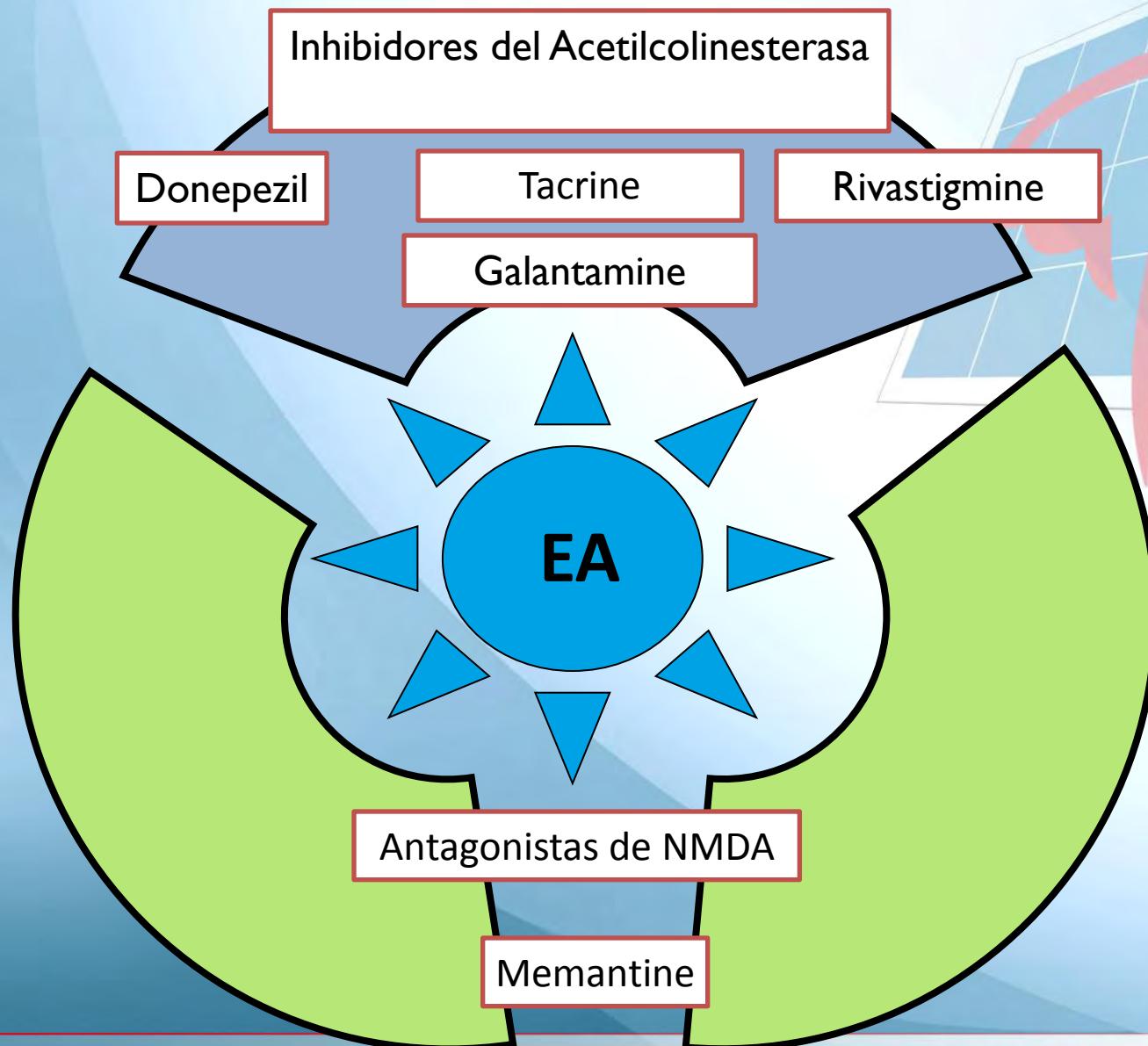
Brain Amyloidogenesis and Potential Therapeutic Interventions



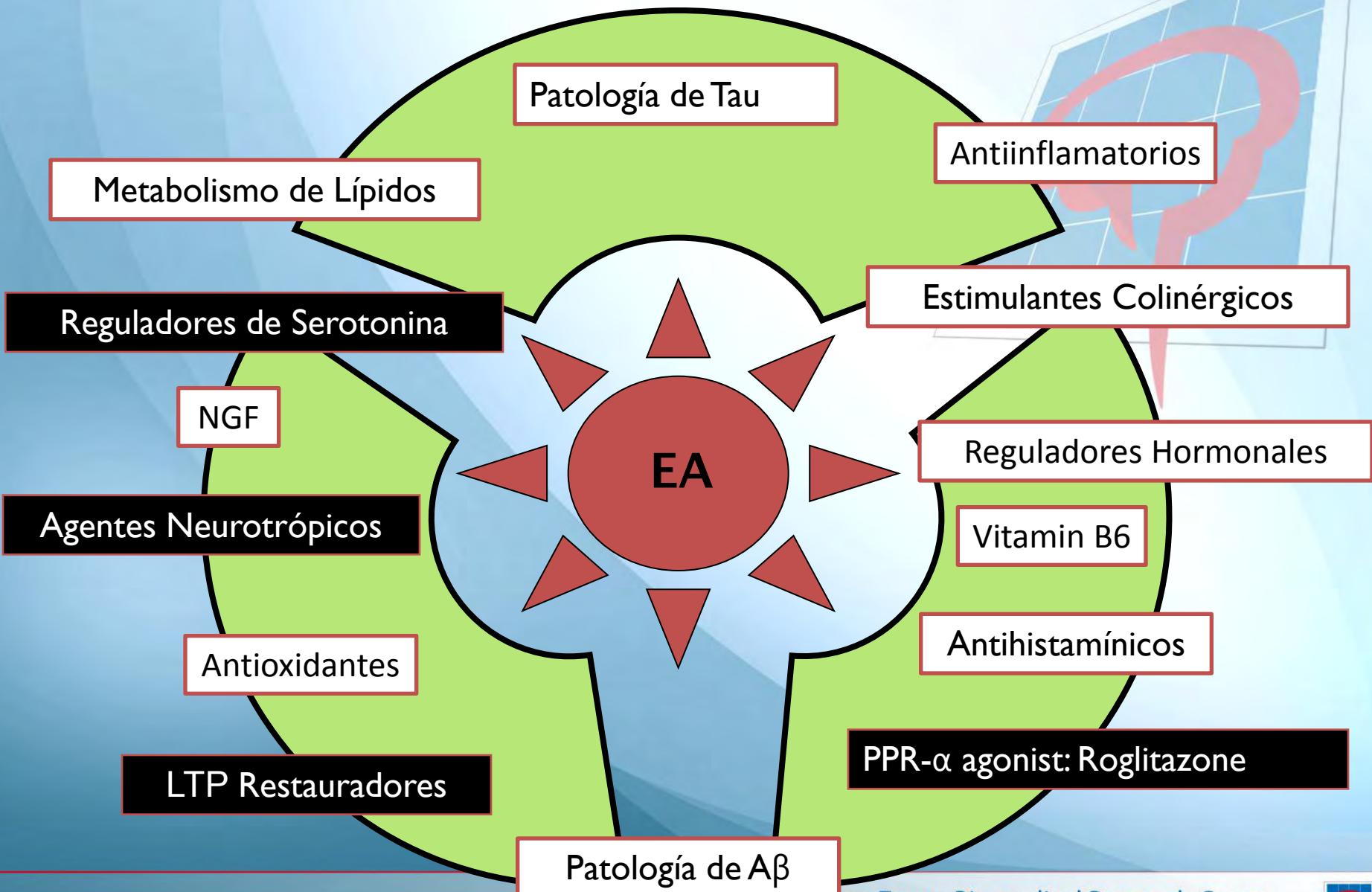
PS2 1q31-q32	TACE 2p25	CASP3 4q35	CTSB 8p22	A2M 12p13.3-p12.3	UB 17p12-p11.1	NOTCH 19p13.2-p13.1	PEN-2 Chr.19
Nicastrin Chr.1	HSPD1 2q33.1	PARK1 4p21	IDE 10q23-q25	LRP1 12q13.1-q13.3	TAU 17q21.1	APOE 19q13.2	PRNP 20pter-p12
APH-1 Chr.1/5	GACE ???	PSMC2 7q22.1-q22.3	BACE 11q23.3	PS1 14q24.3	ACE 17q23	PSMC1 19p13.3	APP 21q21

→ **Genomic Integration**
→ **Gene Therapy**

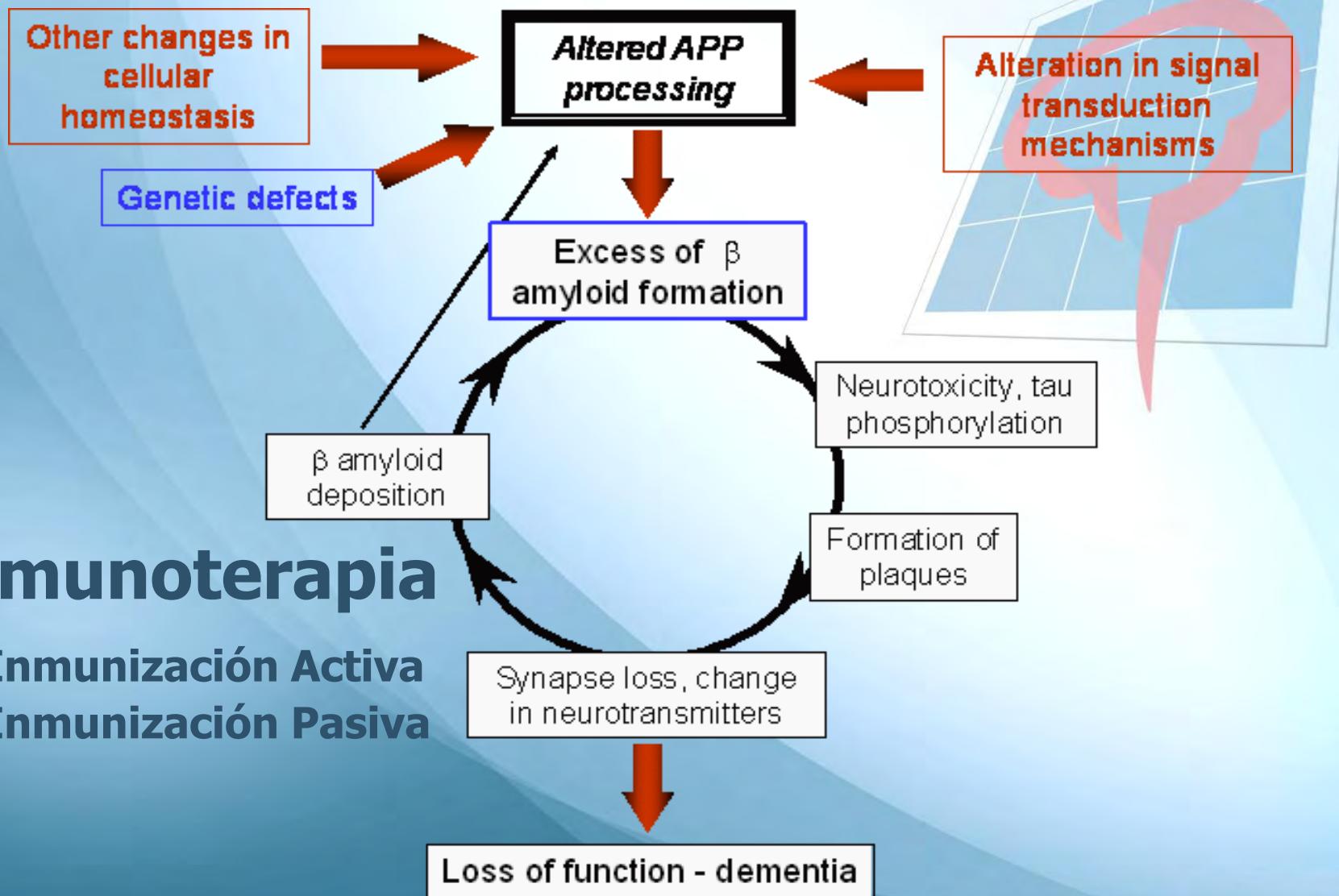
Terapia Actual Anti-Alzheimer



Terapias en Desarrollo Clínico



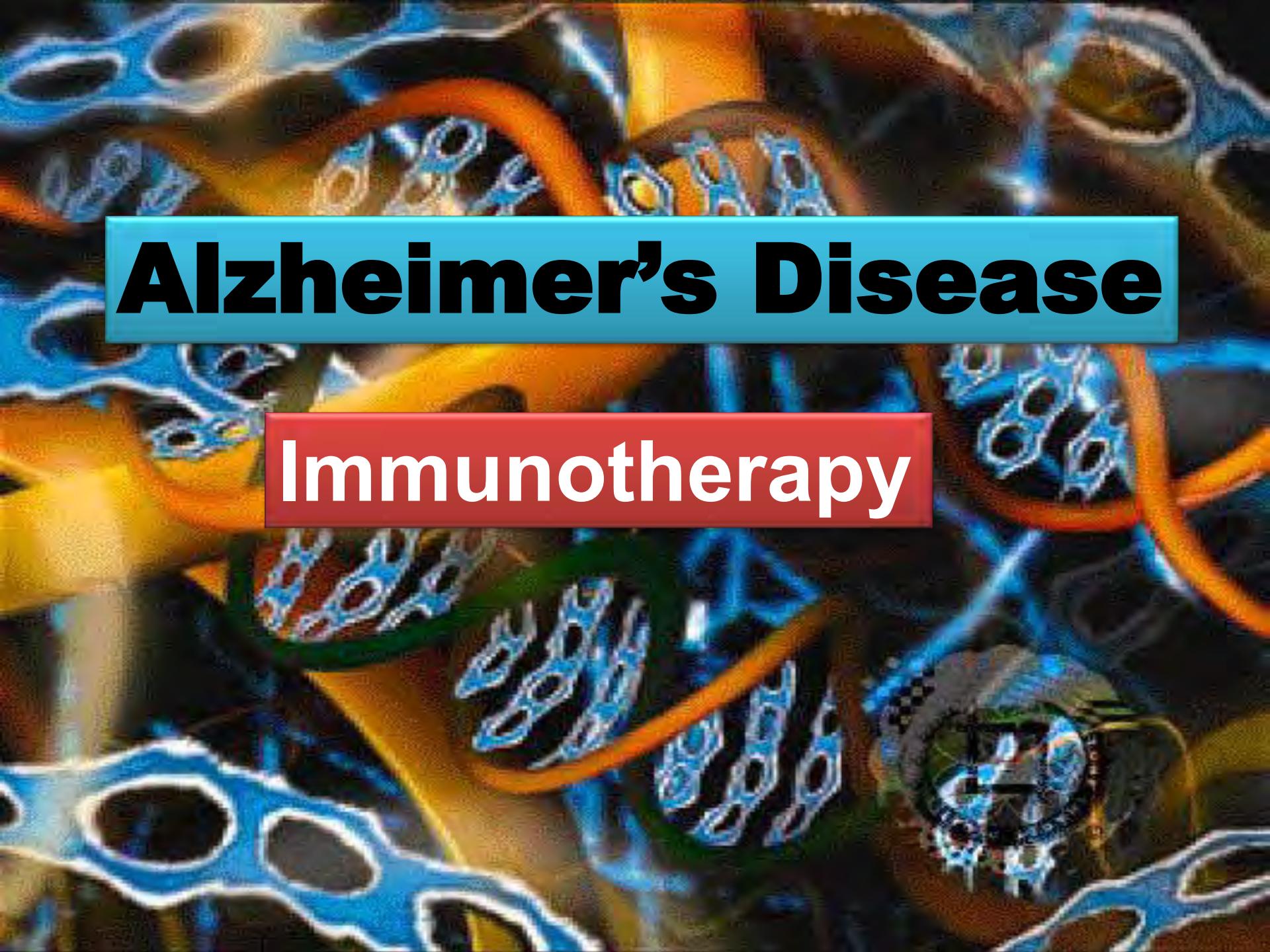
Enfermedad de Alzheimer



Inmunoterapia

Inmunización Activa

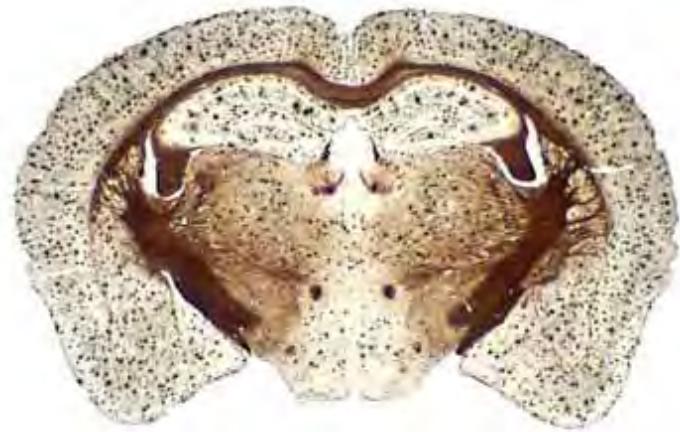
Inmunización Pasiva

A microscopic image showing brain tissue. The image is stained with various colors (blue, yellow, green) to highlight different structures and markers. Several bright, irregularly shaped clusters of blue and white are visible, which are characteristic of neurofibrillary tangles and amyloid plaques found in Alzheimer's disease. The overall texture is somewhat mottled and lacks the normal organized structure of healthy brain tissue.

Alzheimer's Disease

Immunotherapy

Vacuna EuroEspes EB-101



Vacuna EuroEspes EB-101

Diseño Bimodal

Vacuna Preventiva/Profiláctica

Vacuna Terapéutica

Animales Transgénicos

Doble Mutación: APP + PSEN1

Liposomas

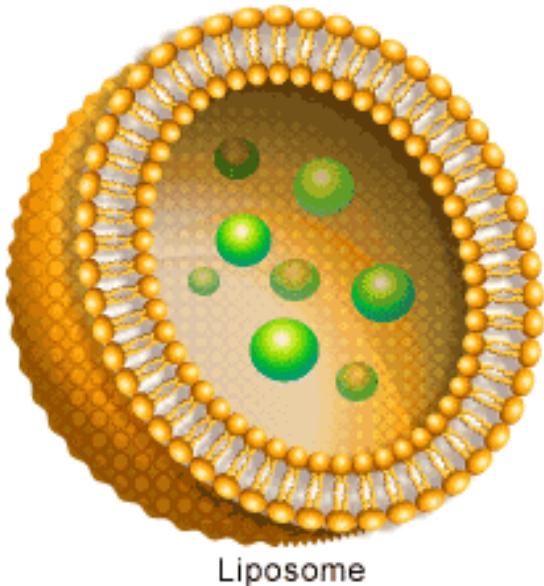
Inmunógeno/Ag: AB1-42

Factor Neurotrófico

S1P (Sphingosine-1-Phosphate)



Vacuna EuroEspes EB-101



Liposomes

1,2-Dioleoyl-sn-Glycero-3-Phosphocholine (DOPC)
1-Palmitoyl-2-oeloyl-sn-glycero-3-phosphatidylglycerol,
Sodium salt (POPG)
Cholesterol (CHO)
+/- D-Erythro-Sphingosine-1-Phosphate (S1P)

Immunogen

Amyloid-Beta 1-42

EB-101



Vacuna EuroEspes EB-101

APPswe/PS1dE9 double-transgenic mice (B6C3F1/J)

Expression of Chimeric mouse/human
Amyloid Precursor Protein (Mo/HuAPP695swe)
and human presenilin 1 (PS1-dE6) mutans



Preventive Protocol (pre-onset)

Age: 7 weeks

EB101: 9 inj 100 uL x 7 months

End: 11 months

Therapeutic Protocol (post-onset)

Age: 35 weeks

EB101: 9 inj 100 uL x 7 months

End: 18 months



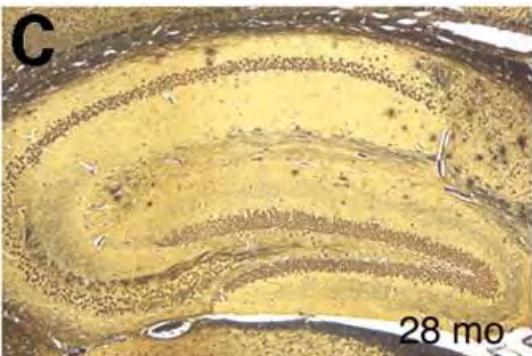
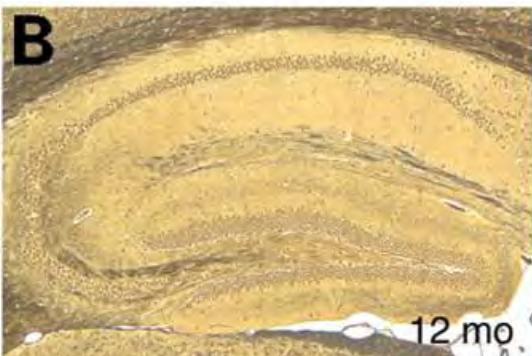
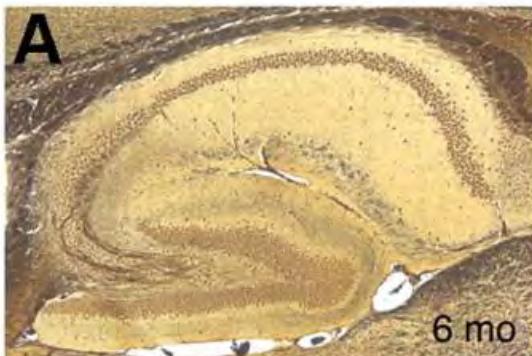
Vacuna EuroEspes EB-101

Early

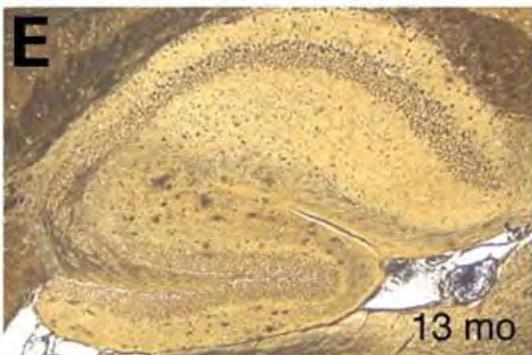
Mid

Late

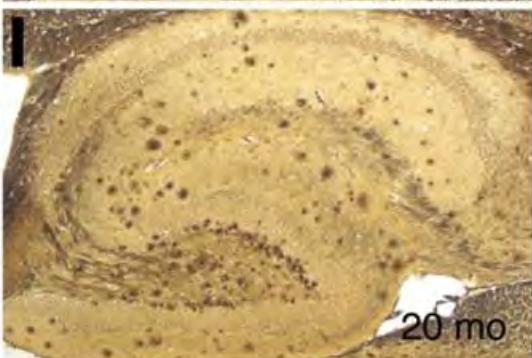
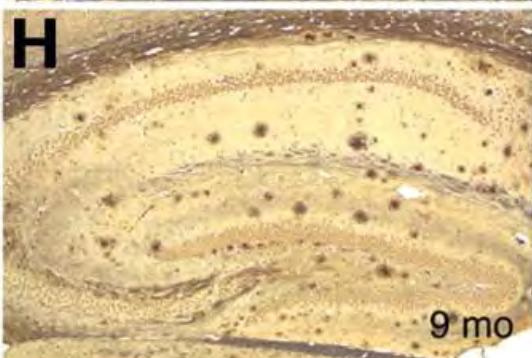
C3-3
(APPswe)



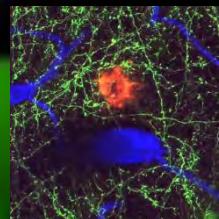
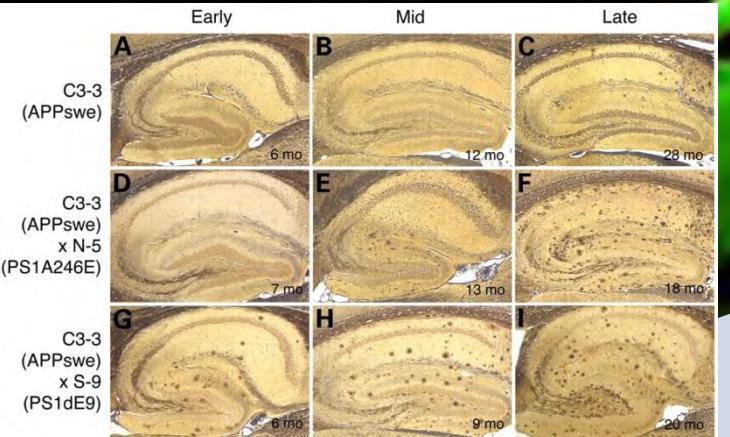
C3-3
(APPswe)
x N-5
(PS1A246E)



C3-3
(APPswe)
x S-9
(PS1dE9)



Vacuna EuroEspes EB-101



Onset
Mild

Severe

Pre-Symptomatic



Therapeutic Vaccination
10-18 months

Preventive Vaccination
2-11 months

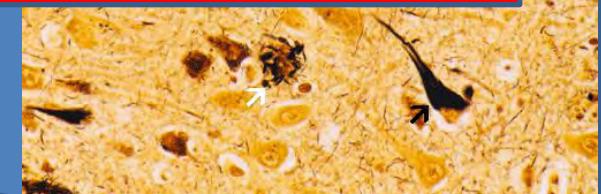
10

0

5

15

20



Vacuna EuroEspes EB-101

Analytical Process

Antibody titers

EB-101 Prophylactic Effects

EB-101 Therapeutic Effects

AD Neuropathological Markers

Immune Response

Behavioral changes

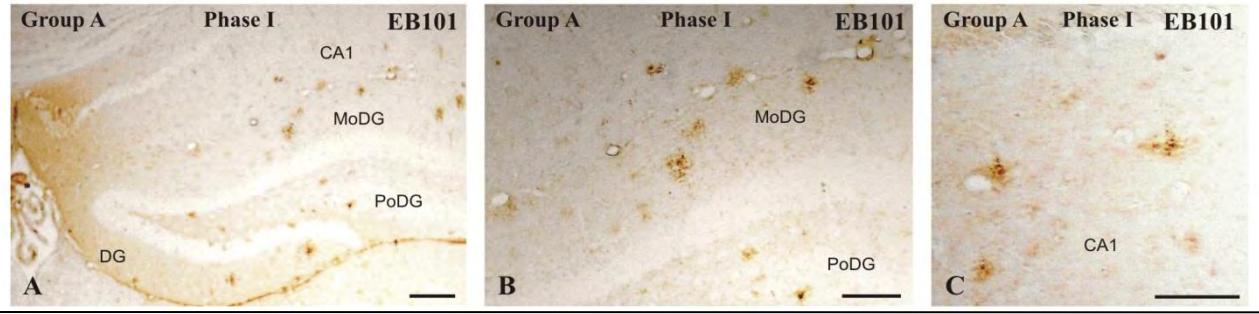


Vacuna EuroEspes EB-101

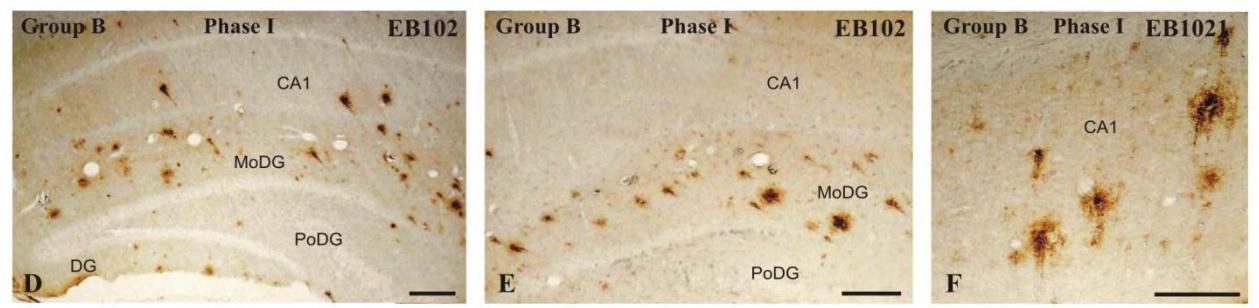
Vacunación Preventiva

Placas de β -amiloide

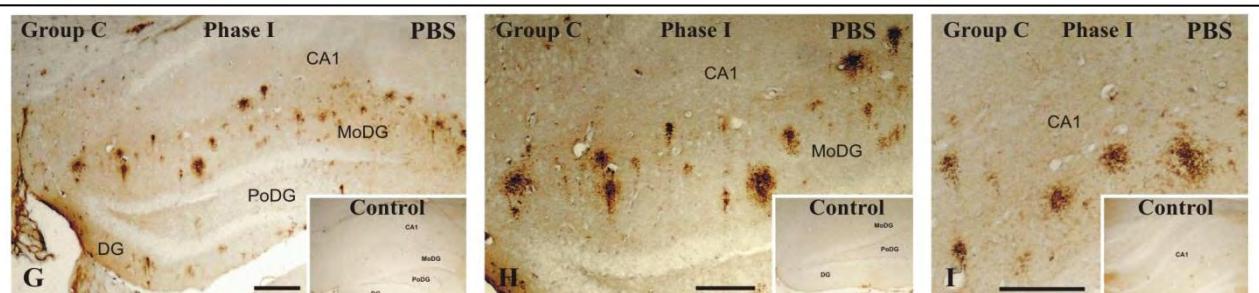
Vacuna



Liposomas



PBS

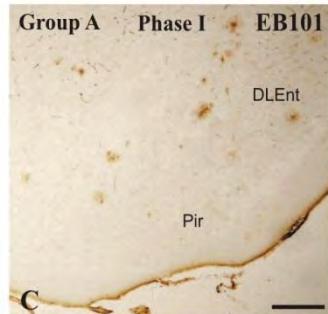
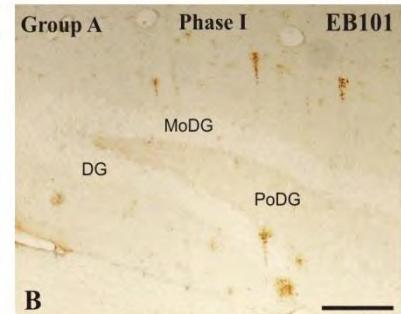
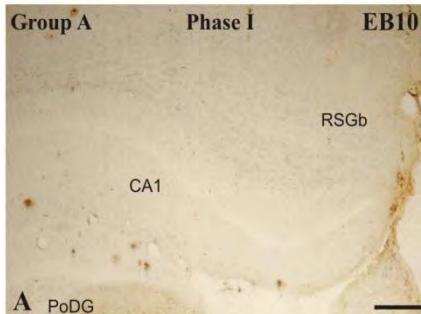


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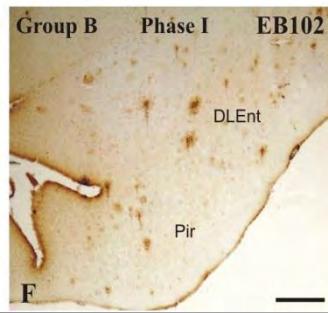
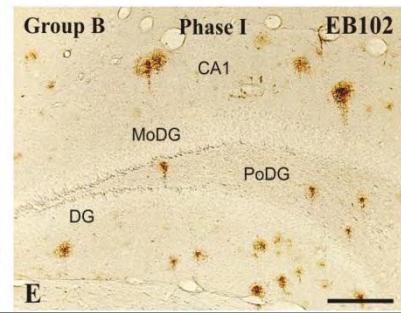
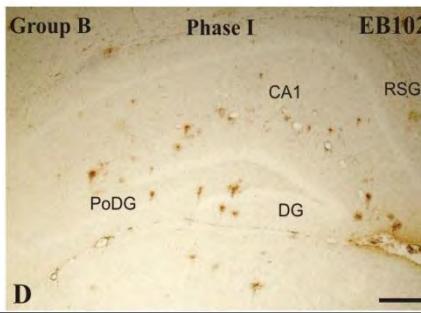
Vacunación Preventiva

Ovillos neurofibrilares

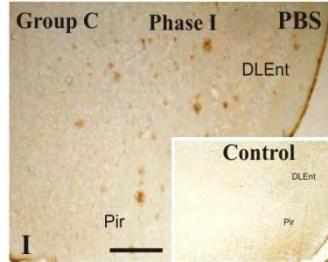
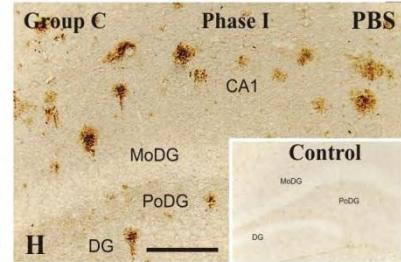
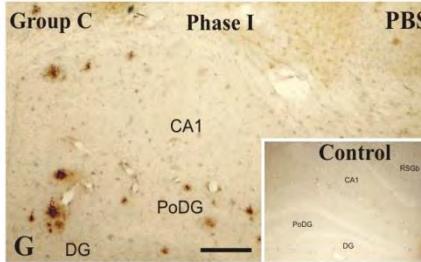
Vacuna



Liposomas



PBS



Vacuna EuroEspes EB-101

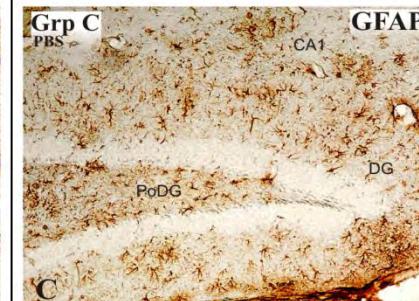
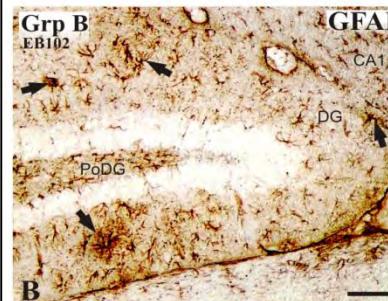
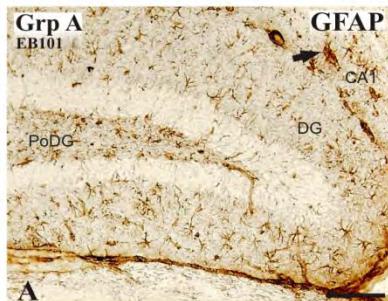
Vacunación Preventiva

Vacuna

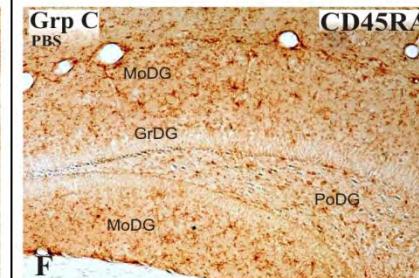
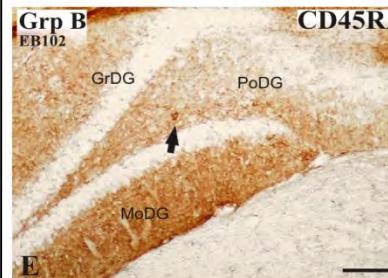
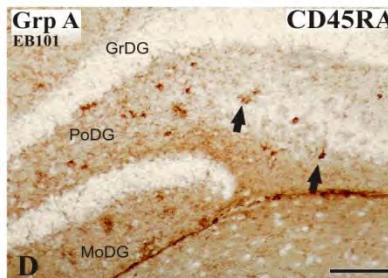
Liposomas

PBS

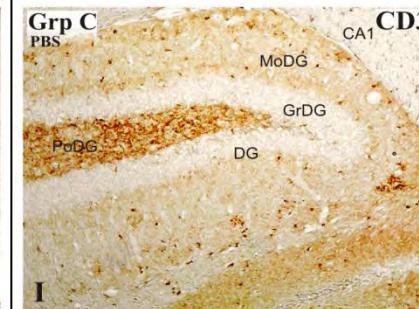
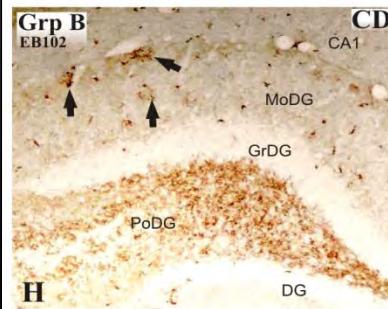
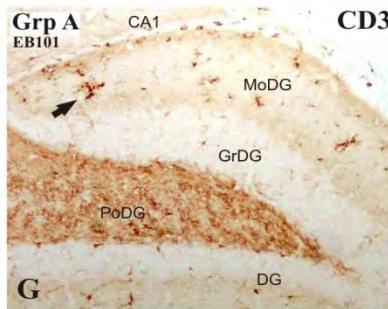
GFAP - astroglia



CD45 - linf B



CD3 - linf T

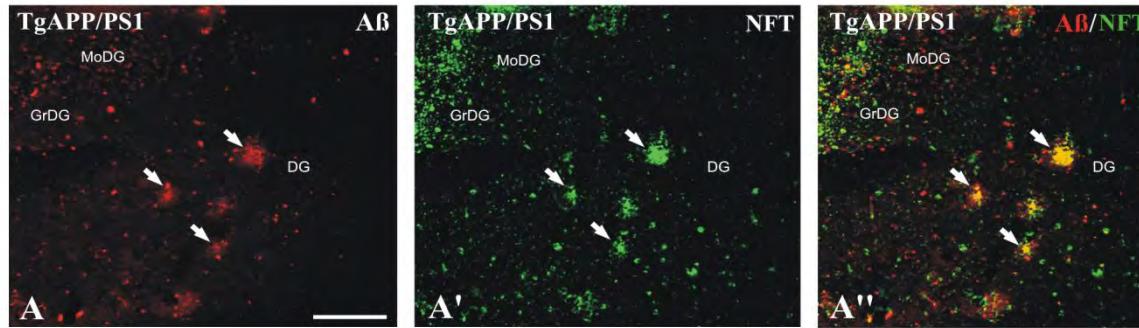


Vacuna EuroEspes EB-101

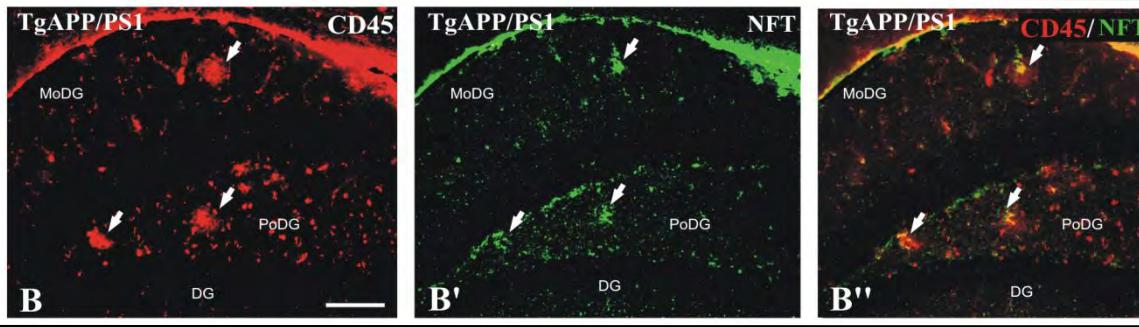
Vacunación Preventiva

Relación entre biomarcadores

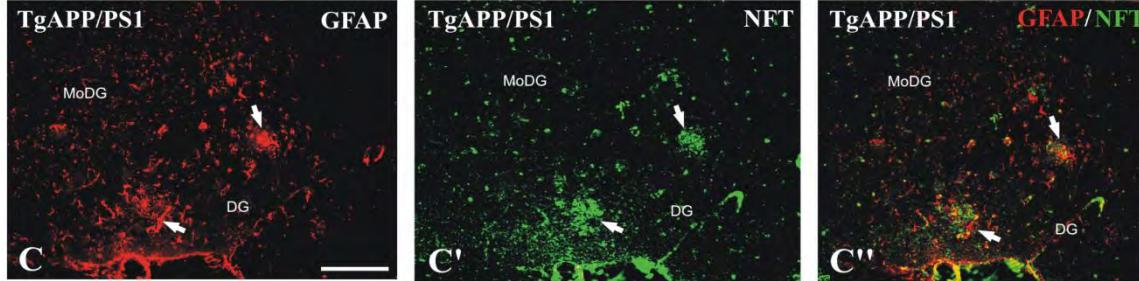
A β /NFT



CD45/NFT



GFAP/NFT

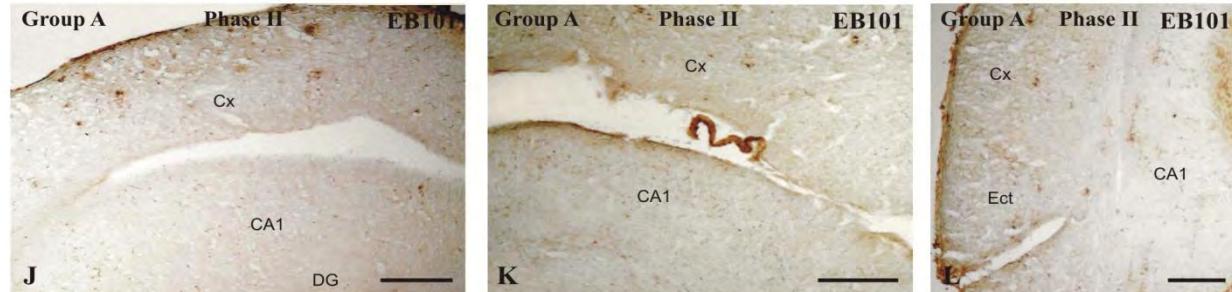


Vacuna EuroEspes EB-101

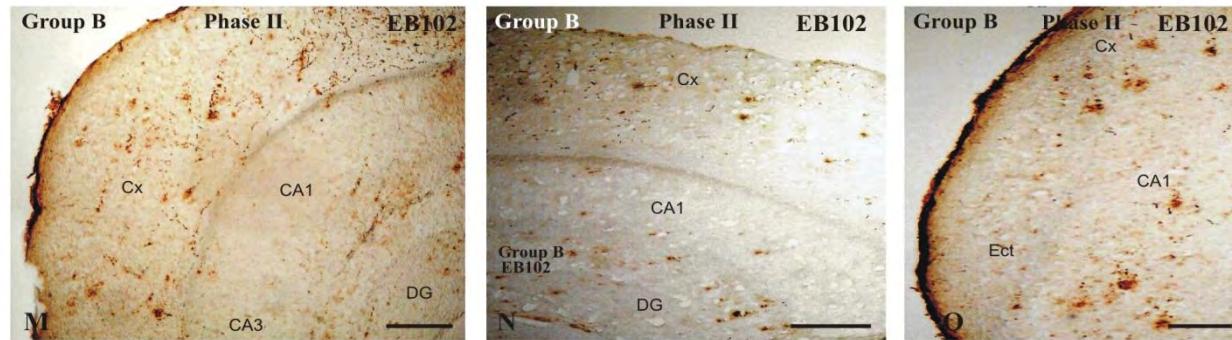
Vacunación Terapéutica

Placas de β -amiloide

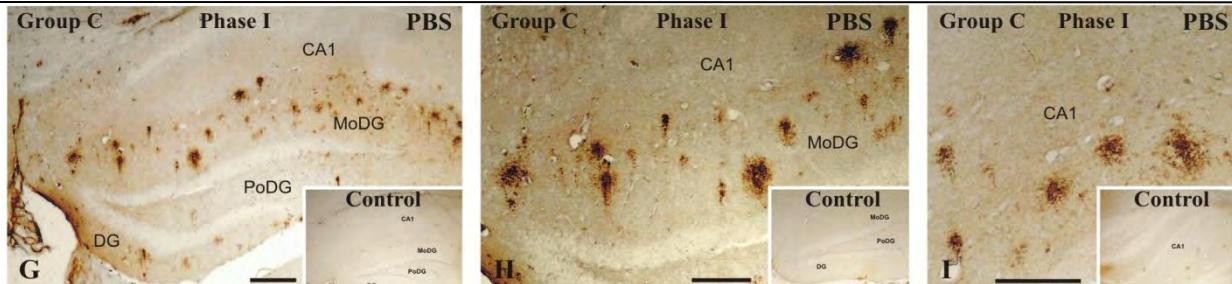
Vacuna



Liposomas



PBS

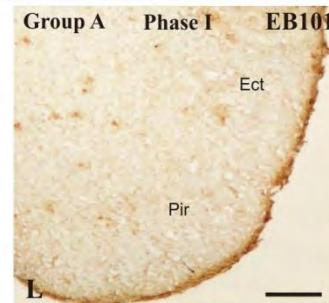
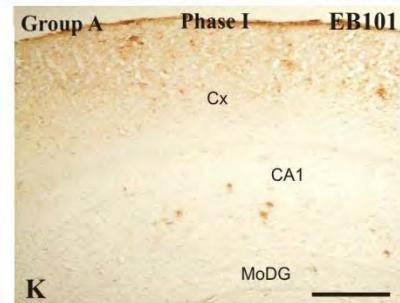
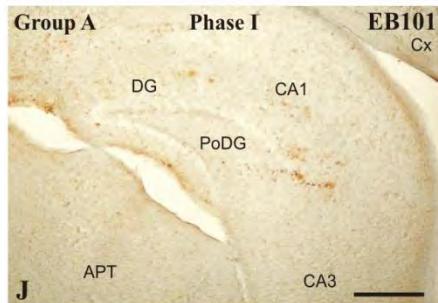


Vacuna EuroEspes EB-101

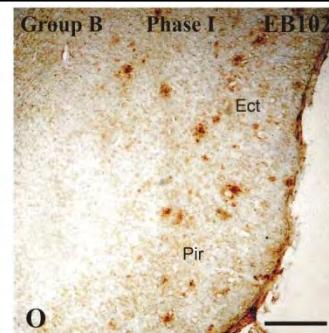
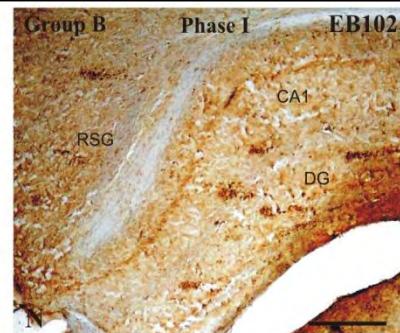
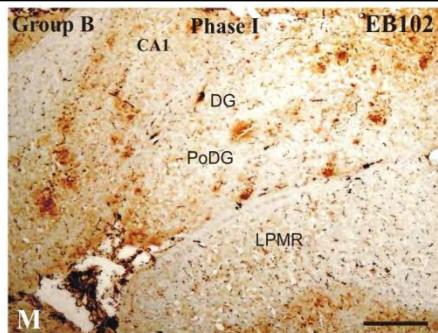
Vacunación Terapéutica

Ovillos neurofibrilares

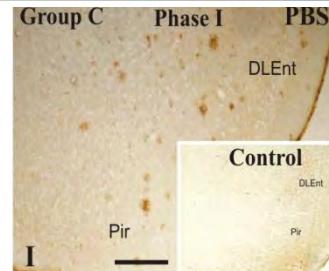
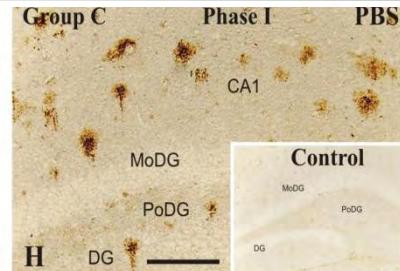
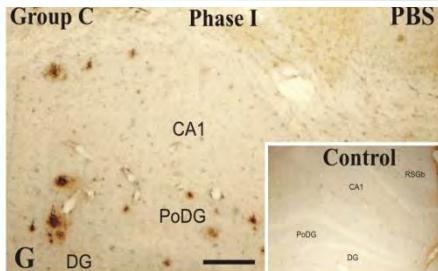
Vacuna



Liposomas

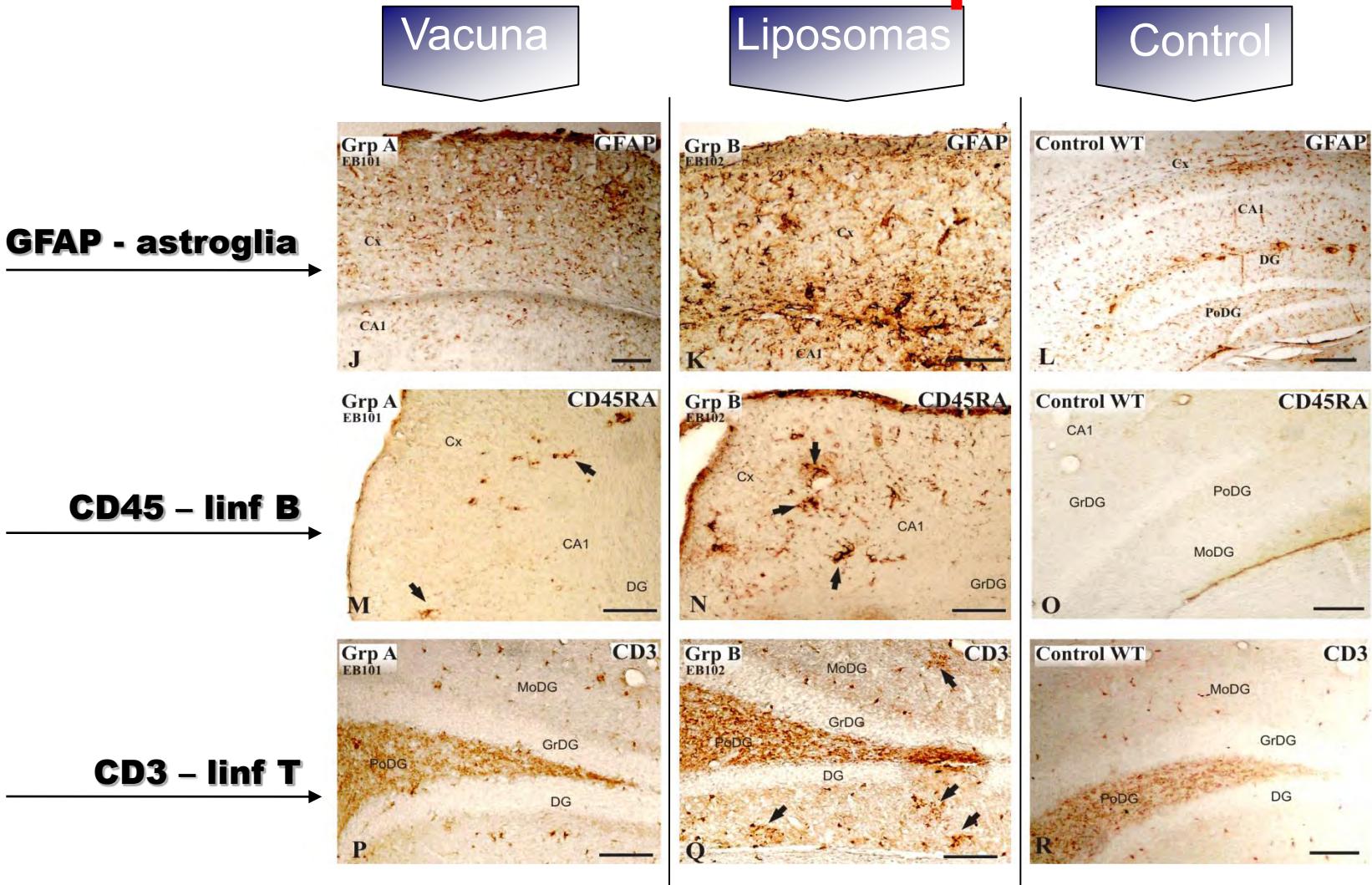


PBS



Vacuna EuroEspes EB-101

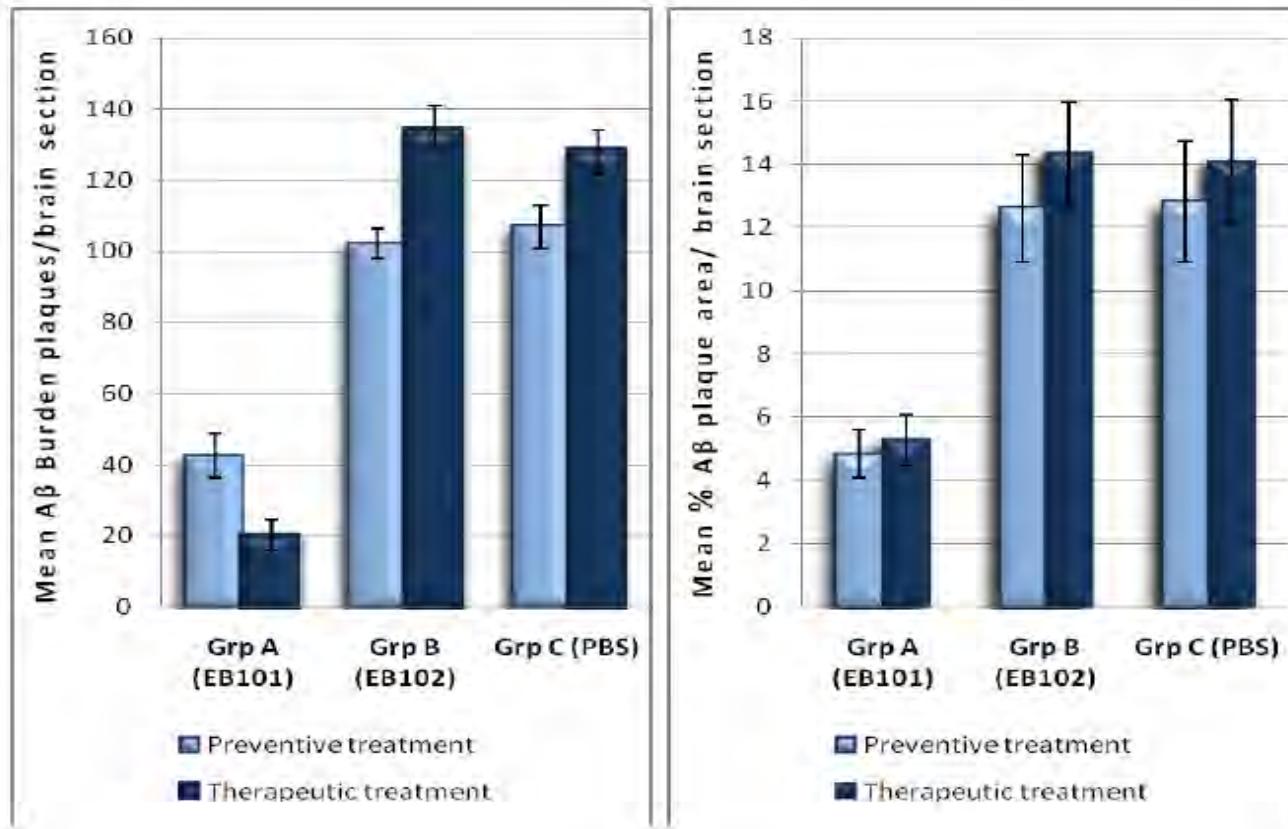
Vacunación Terapéutica



Vacuna EuroEspes EB-101

Vacunación Preventiva+Terapéutica

Reducción de Proceso Amiloidogénico



PHARMACOGENETICS

Genetic Polymorphisms

Pharmacokinetics
Absorption
Distribution
Metabolism
Excretion

Safety

Pharmacodynamics
Receptors
Ion channels
Enzymes
Proteins

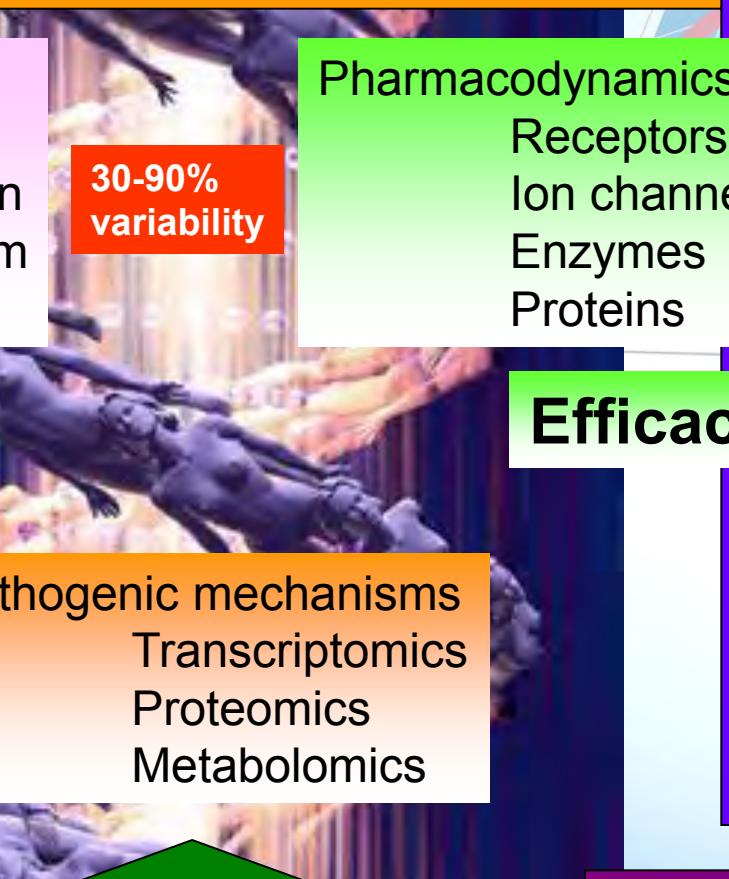
Efficacy

Pathogenic mechanisms
Transcriptomics
Proteomics
Metabolomics

Metabolism

DRUGS

Disease



Genomics Orchestra

Drugs

Genes

Disease

Pharmacogenomics



Pathogenic Genes

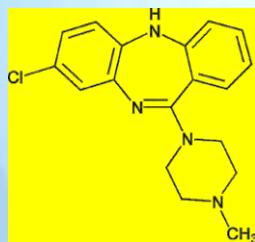
Drug Action

Drug Metabolism

Drug Transporters

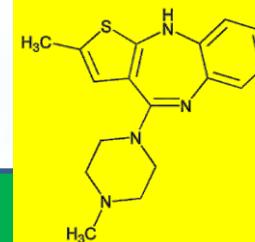
Pleiotropic Genes

Substrates



Mechanism of Action

Drug Metabolism

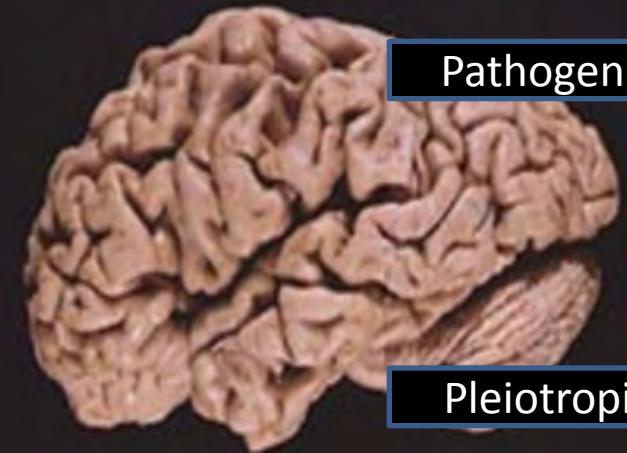


Inhibitors

Inducers

Treatment

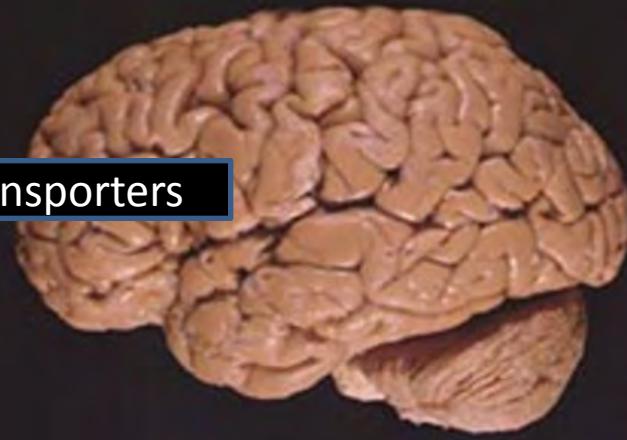
Disease



Pathogenic genes



Drug Transporters



Phenotype-A

Surrogate markers
Biomarkers

Genomics

Genotype

Phenotype-B

Transcriptomics
Proteomics
Metabolomics

Disease/Phenotype Modification

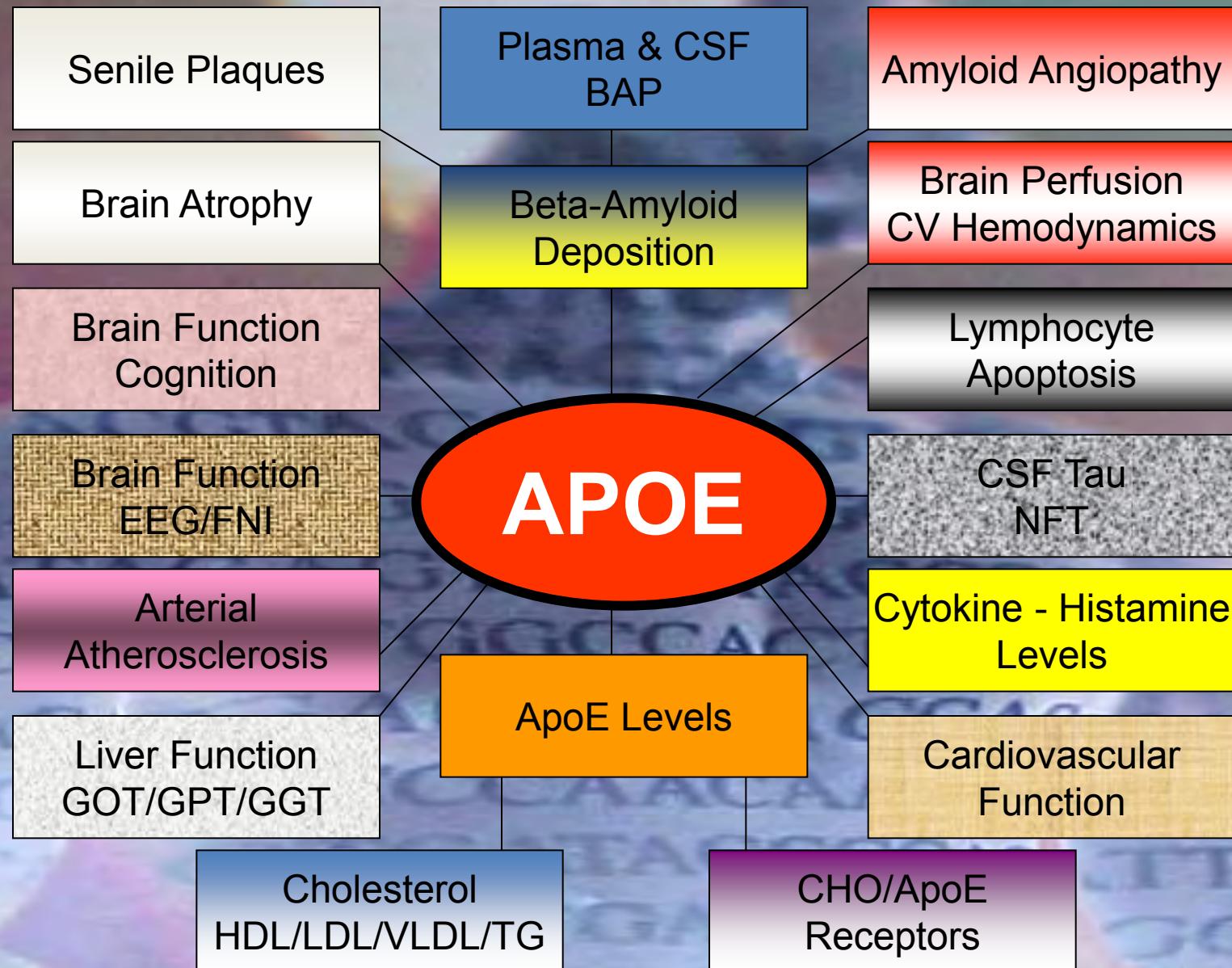


Genomics of Pleiotropic Genes

APOE

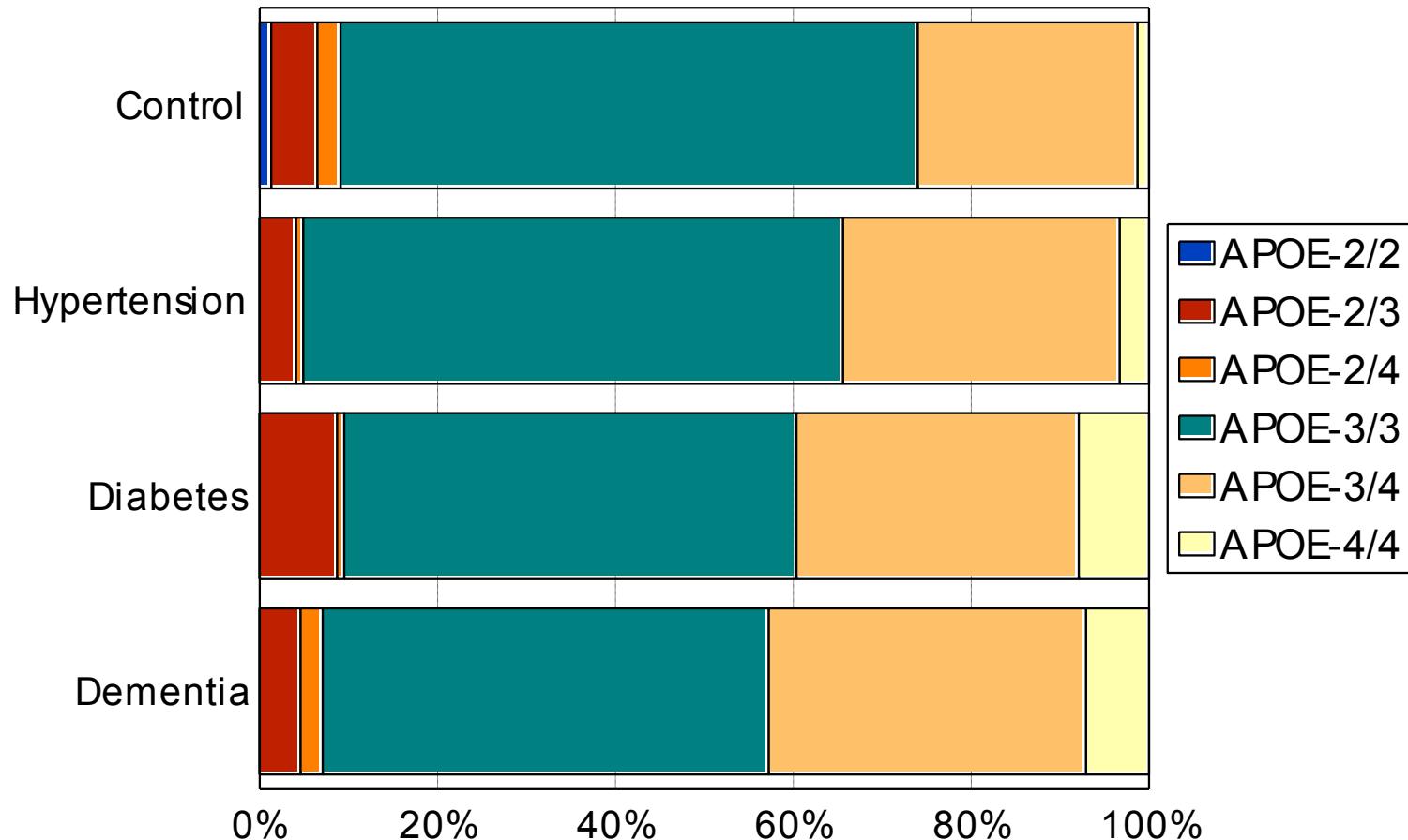


Influence of APOE genotypes on Alzheimer's disease-related phenotypes



APOE Genotype Distribution

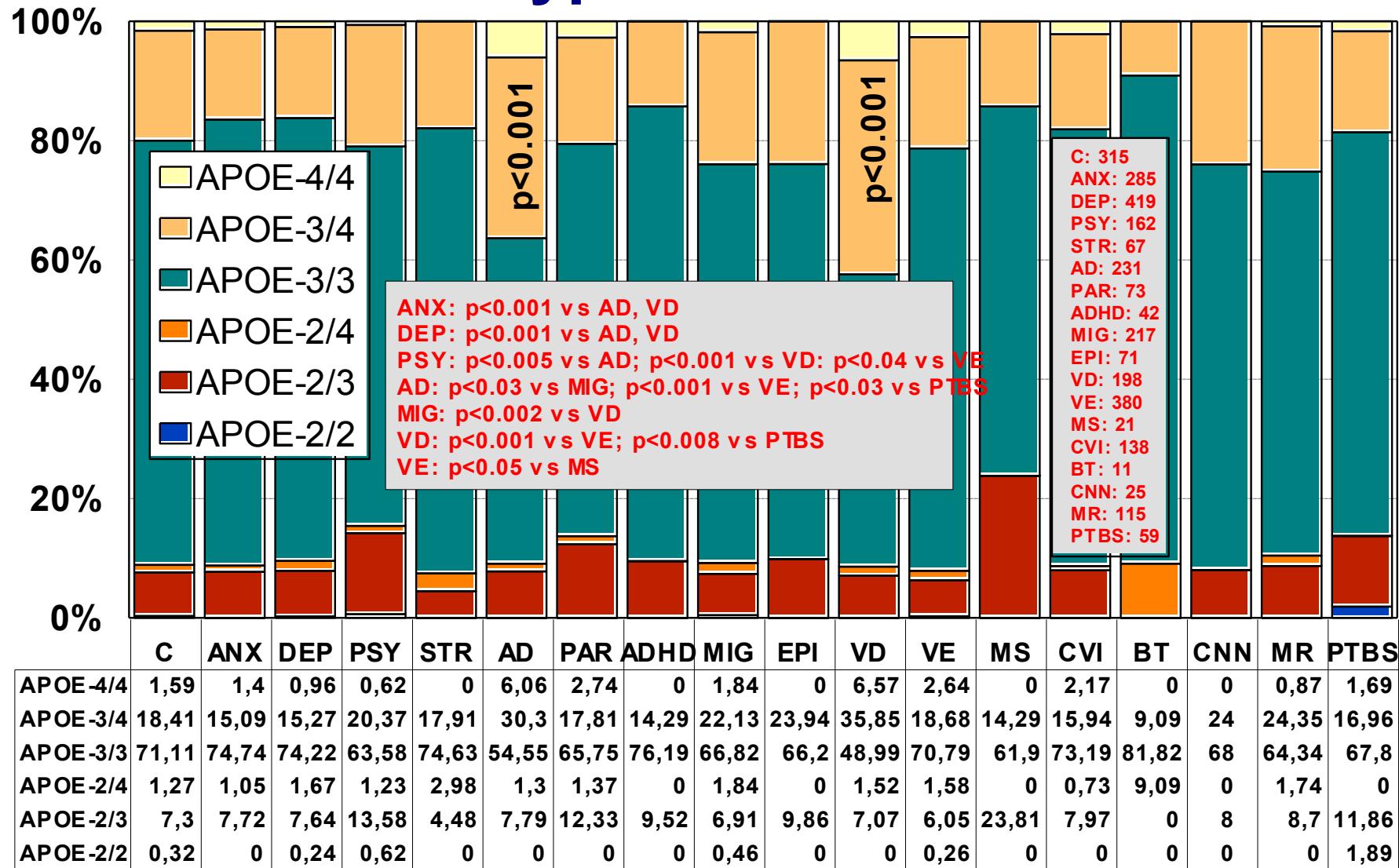
APOE Distribution in Hypertension, Diabetes and Dementia

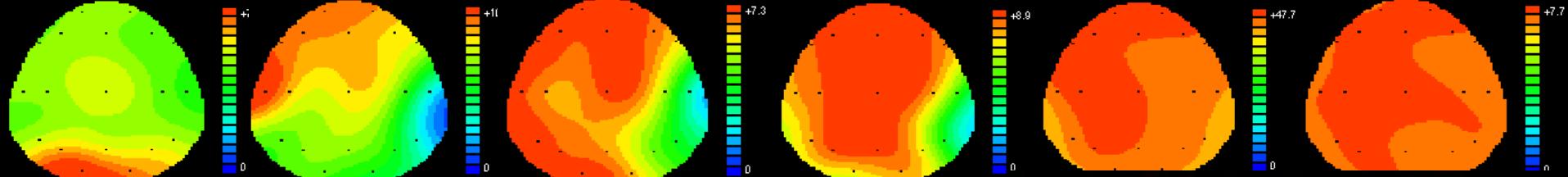


Cacabelos et al., EuroEspes Biomedical Research Center, 2000



APOE Genotypes in CNS Disorders





Control

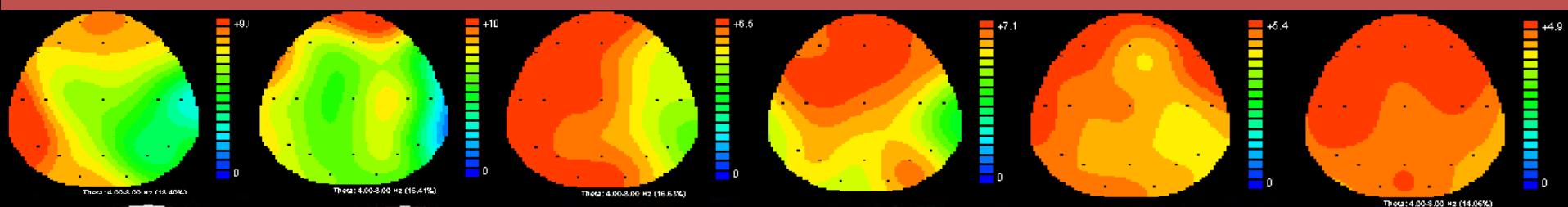
GDS-3

GDS-4

GDS-5

GDS-6

GDS-7



APOE-2/2

APOE-2/3

APOE-2/4

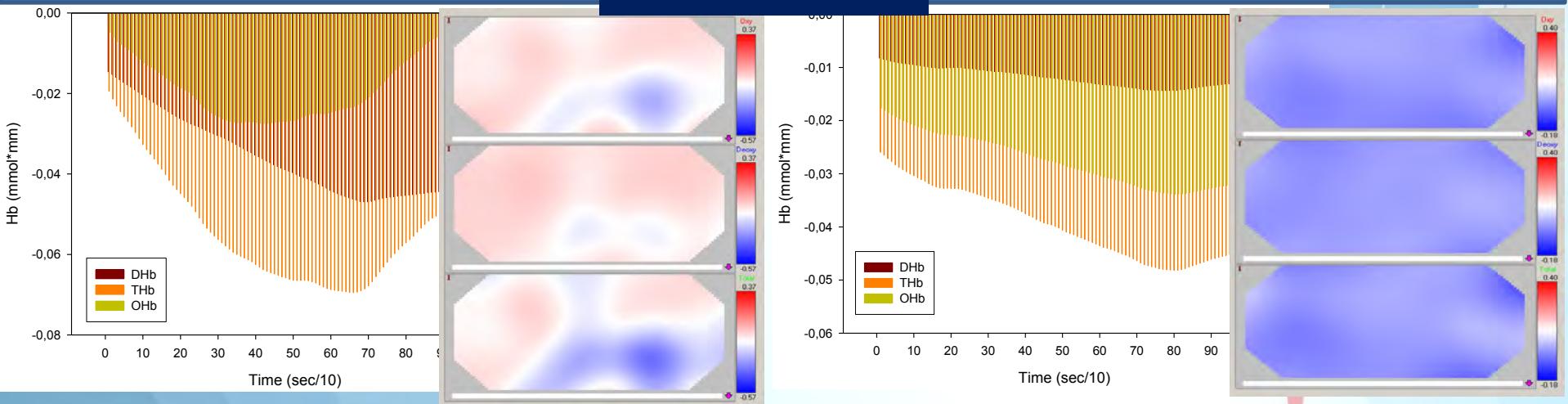
APOE-3/3

APOE-3/4

APOE-4/4

APOE-Related Brain Optical Topography Changes

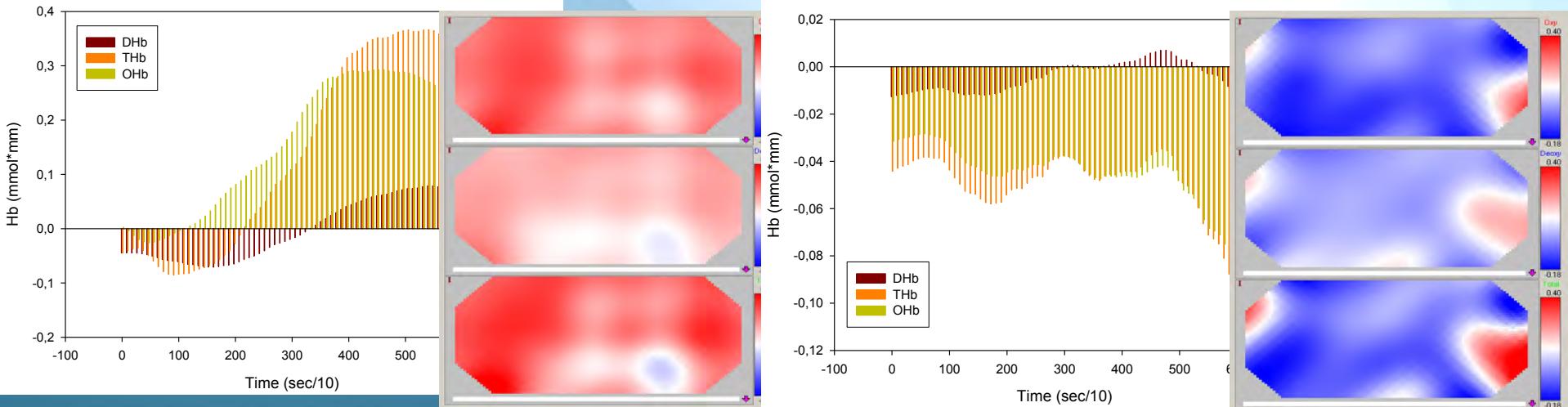
Basal Conditions



AD-APOE-3/3

AD-APOE-4/4

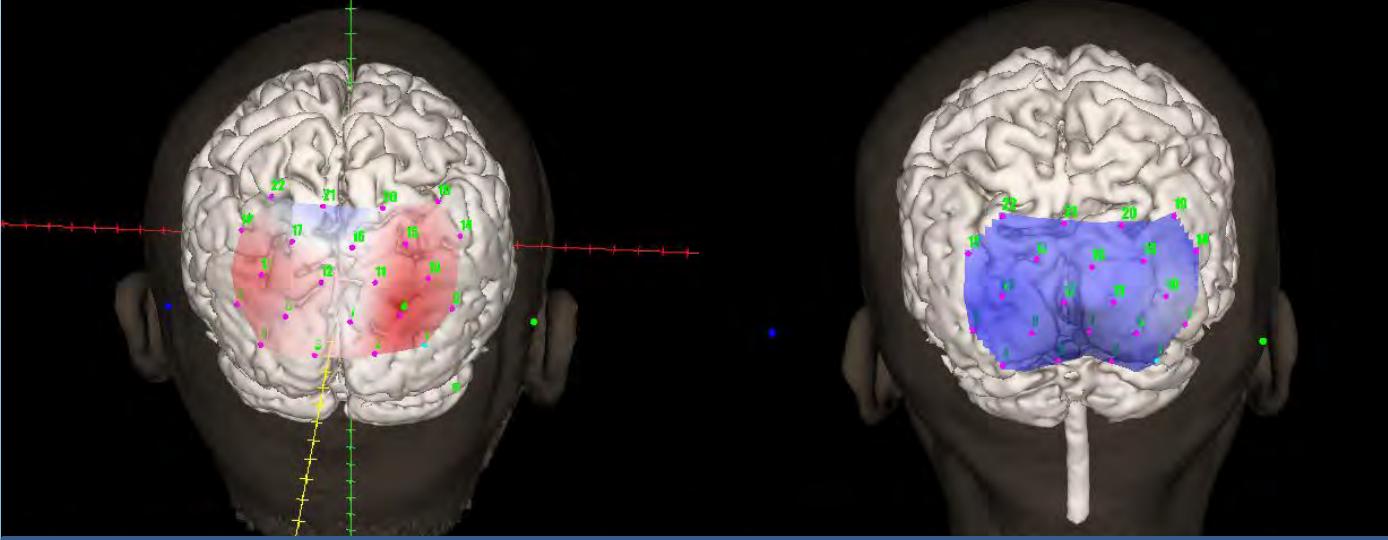
Visual Stimulation



Cacabelos et al (2008)

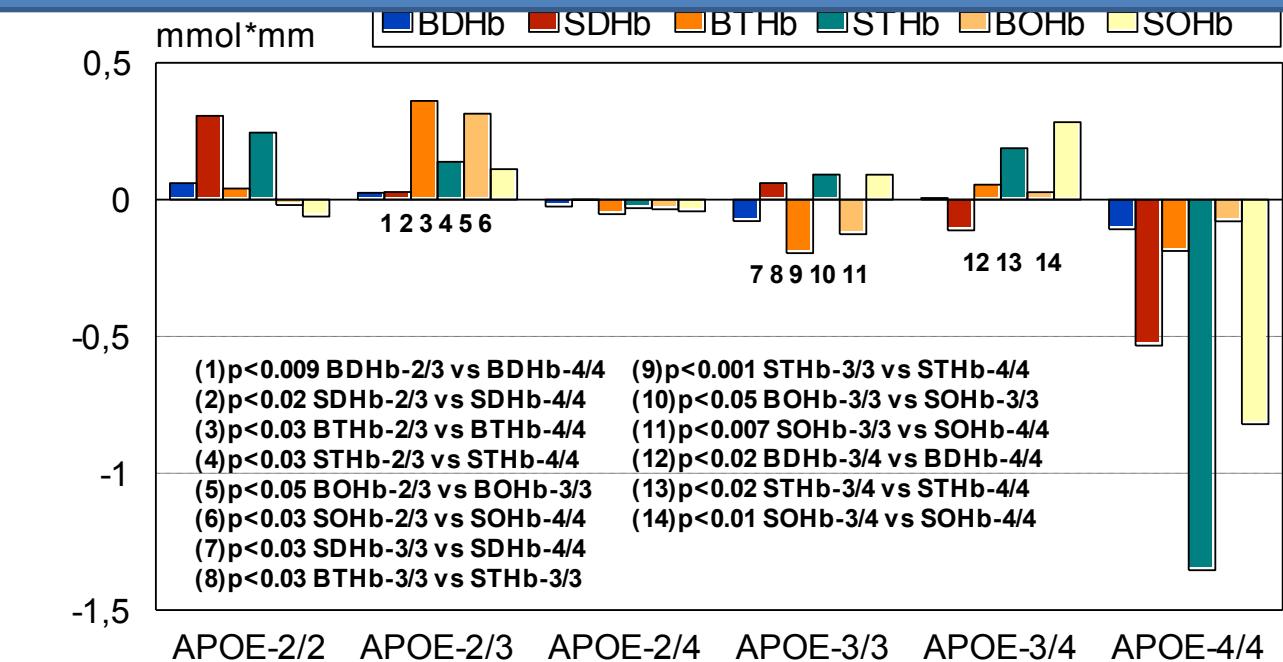
EuroEspes Biomedical Research Center
Institute for CNS Disorders and Genomic Medicine



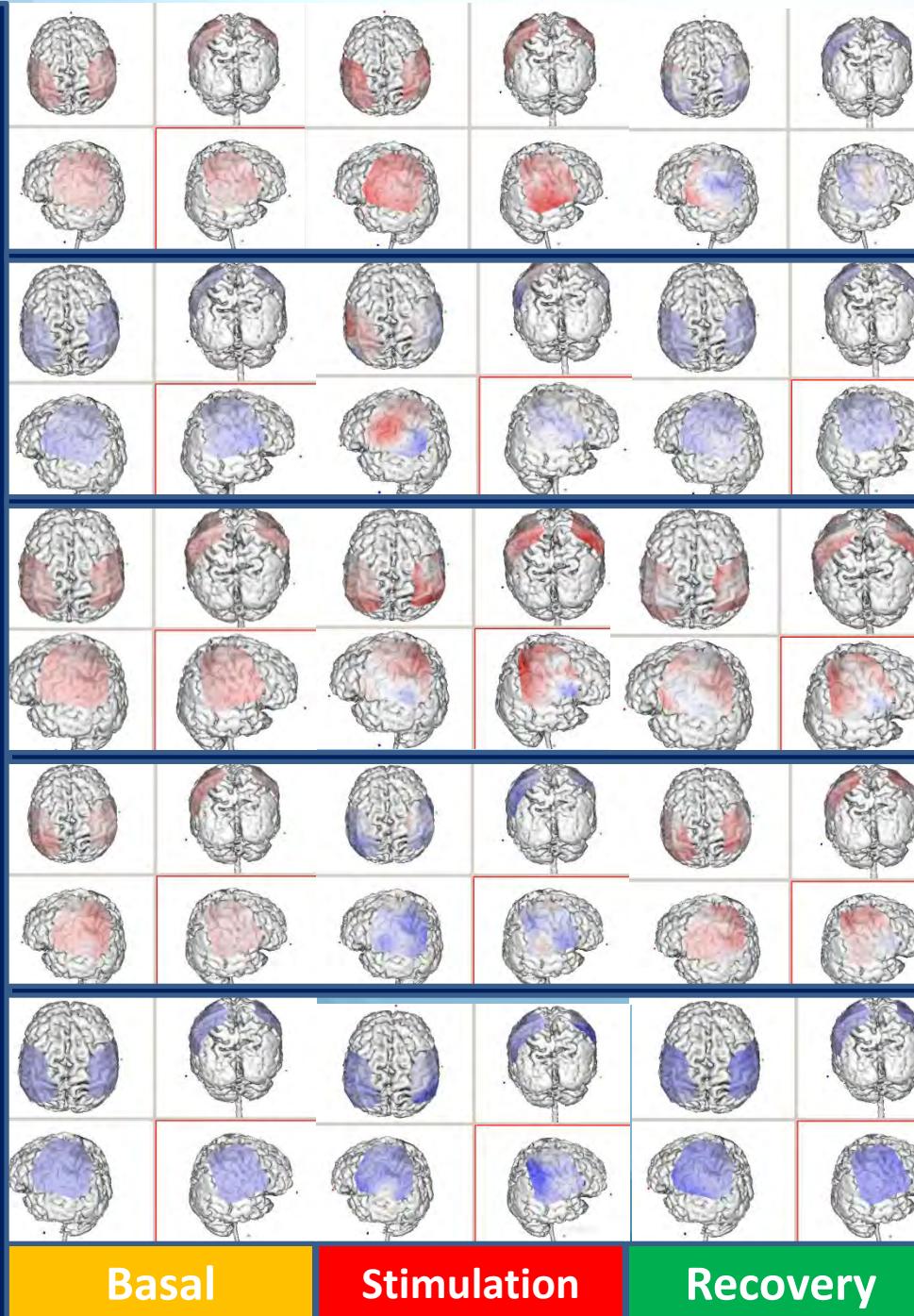


APOE-3/3

APOE-4/4



Optical Brain Topography



APOE-2/3

APOE-2/4

APOE-3/3

APOE-3/4

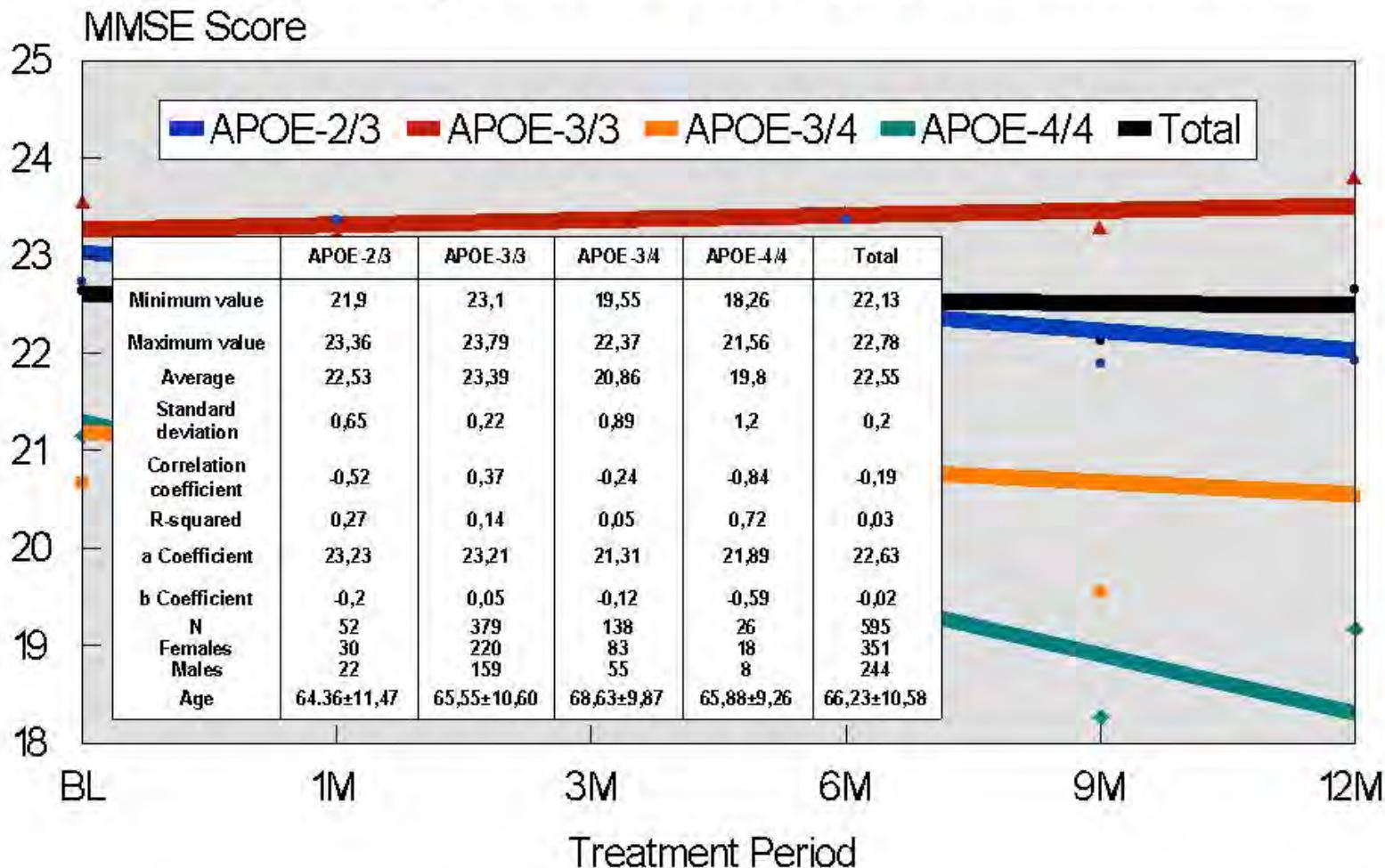
APOE-4/4

Biomedical Research Center
Institute for CNS Disorders and Genomic Medicine

APOE Genotype-Related
Cortical DOT Hemoglobin Consumption

APOE Pharmacogenomics

APOE-Related Therapeutic Response to a Multifactorial Treatment in patients with Alzheimer's Disease



CYP2D6+CYP2C19+CYP2C9 Clusters

CYP2D6+CYP2C19+CYP2C9 Clustered Phenotypes in Alzheimer's Disease



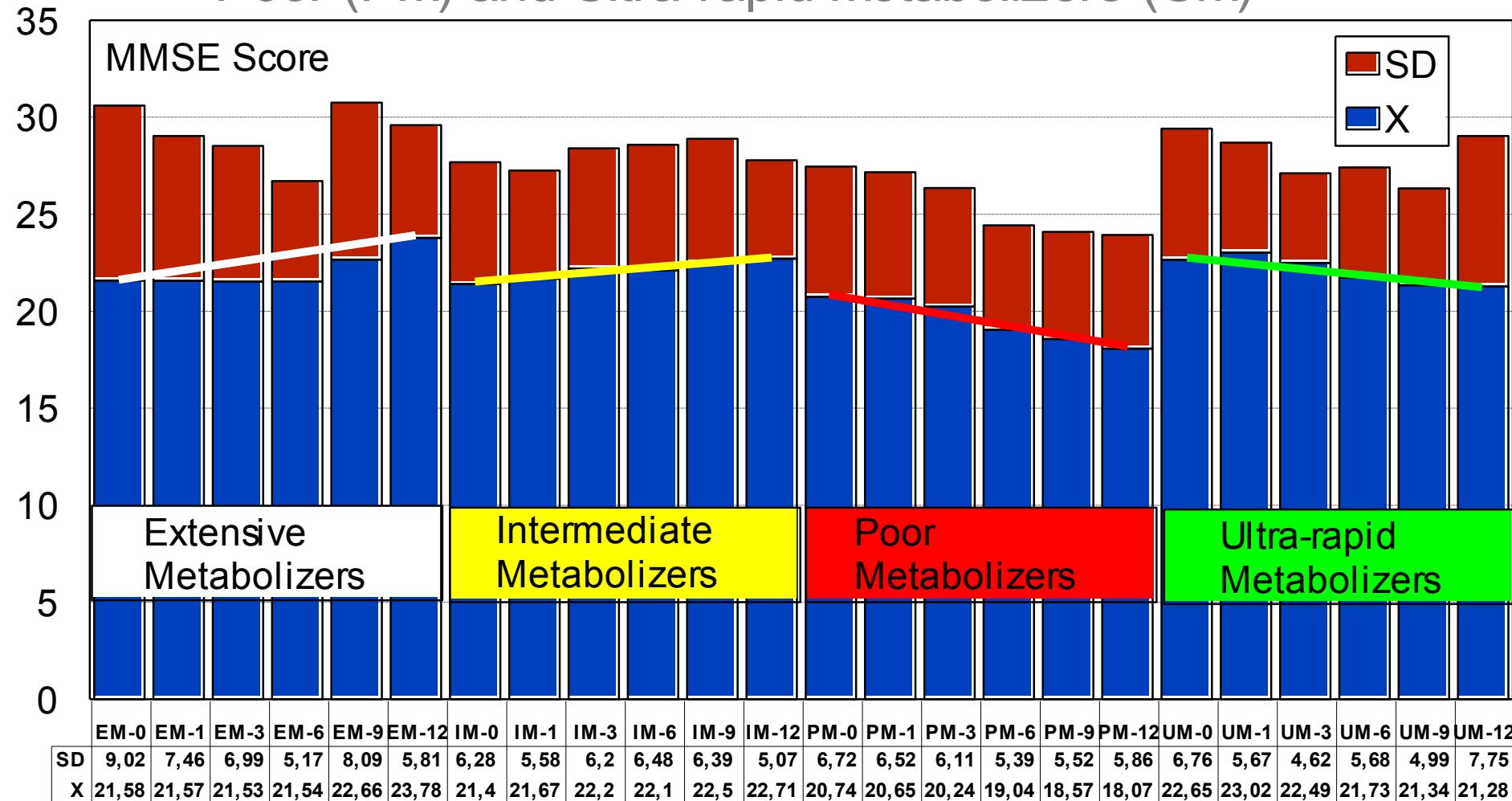
Phenotype	N	%
EM+EM+EM	416	26,513703
EM+EM+IM	240	15,2963671
EM+EM+PM	49	3,12300829
EM+IM+EM	167	10,6437221
EM+IM+IM	56	3,56915233
EM+IM+PM	1	0,06373486
EM+PM+EM	10	0,63734863
EM+PM+IM	0	0
EM+PM+PM	0	0
IM+EM+EM	171	10,9986616
IM+EM+IM	135	8,6042065
IM+EM+PM	16	1,01975781
IM+PM+PM	0	0
IM+IM+EE	105	6,69216061
IM+IM+IM	32	2,03951562
IM+IM+PM	0	0
IM+PM+EM	1	0,06373486
IM+PM+IM	5	0,31867431
IM+PM+PM	0	0
PM+EM+EM	25	1,59337157
PM+EM+IM	18	1,14722753
PM+EM+PM	7	0,44614404
PM+EM+IM	8	0,5098789
PM+EM+PM	8	0,5098789
PM+IM+EM	0	0
PM+IM+IM	2	0,12746973
PM+IM+PM	0	0
PM+PM+EM	43	2,74059911
PM+PM+IM	30	1,91204589
PM+PM+PM	4	0,25493945
UM+EM+EM	14	0,89228808
UM+EM+IM	6	0,38240918
UM+EM+PM	0	0
UM+PM+EM	0	0
UM+PM+IM	0	0
UM+PM+PM	0	0

Ramón Cacabelos, EuroEspes Pharmacogenomics Programme (2005-2010)



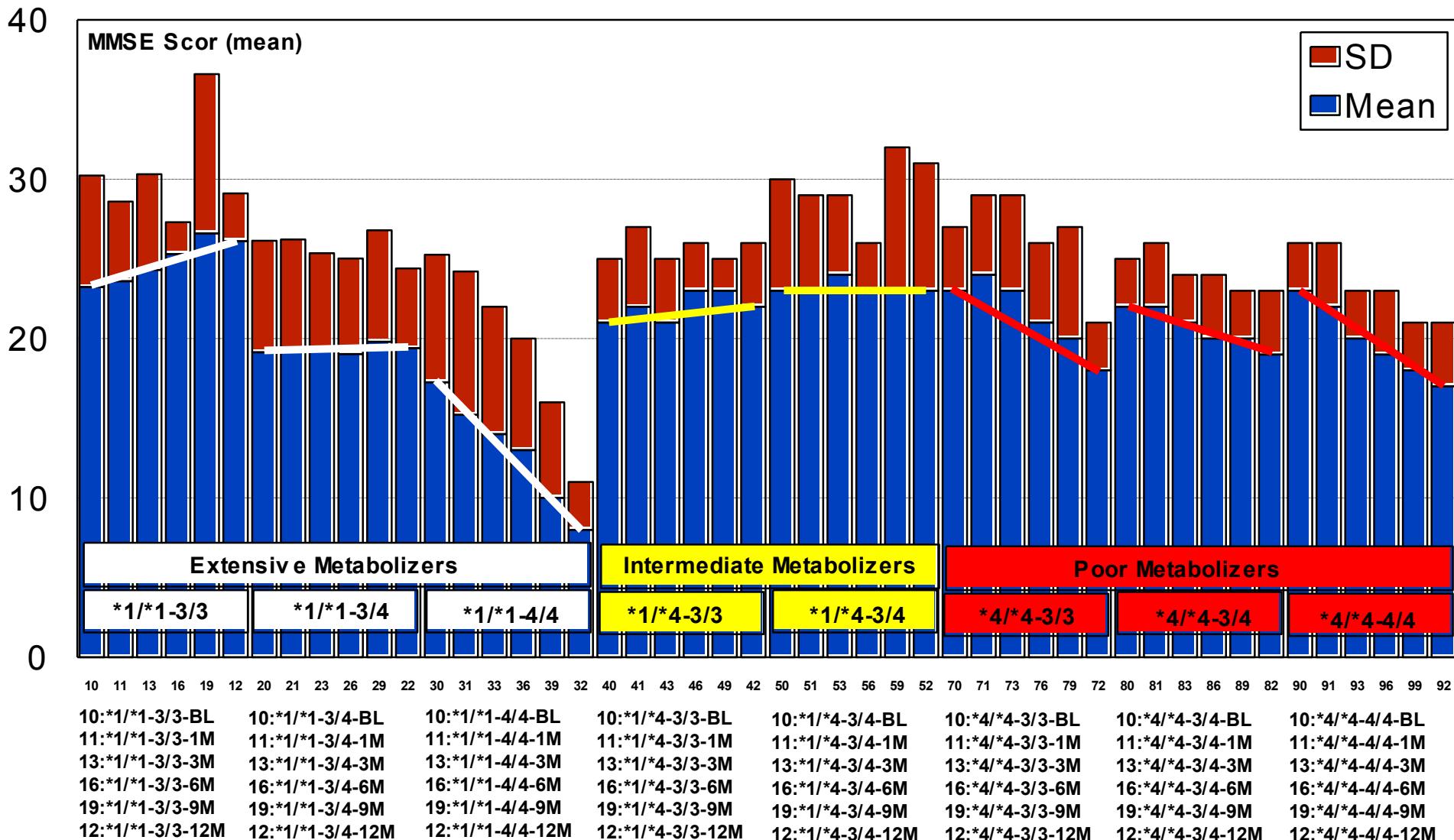
CYP2D6-Related Therapeutic Response in Alzheimer's Disease

Cognitive Performance in Extensive (EM), Intermediate (IM),
Poor (PM) and Ultra-rapid Metabolizers (UM)

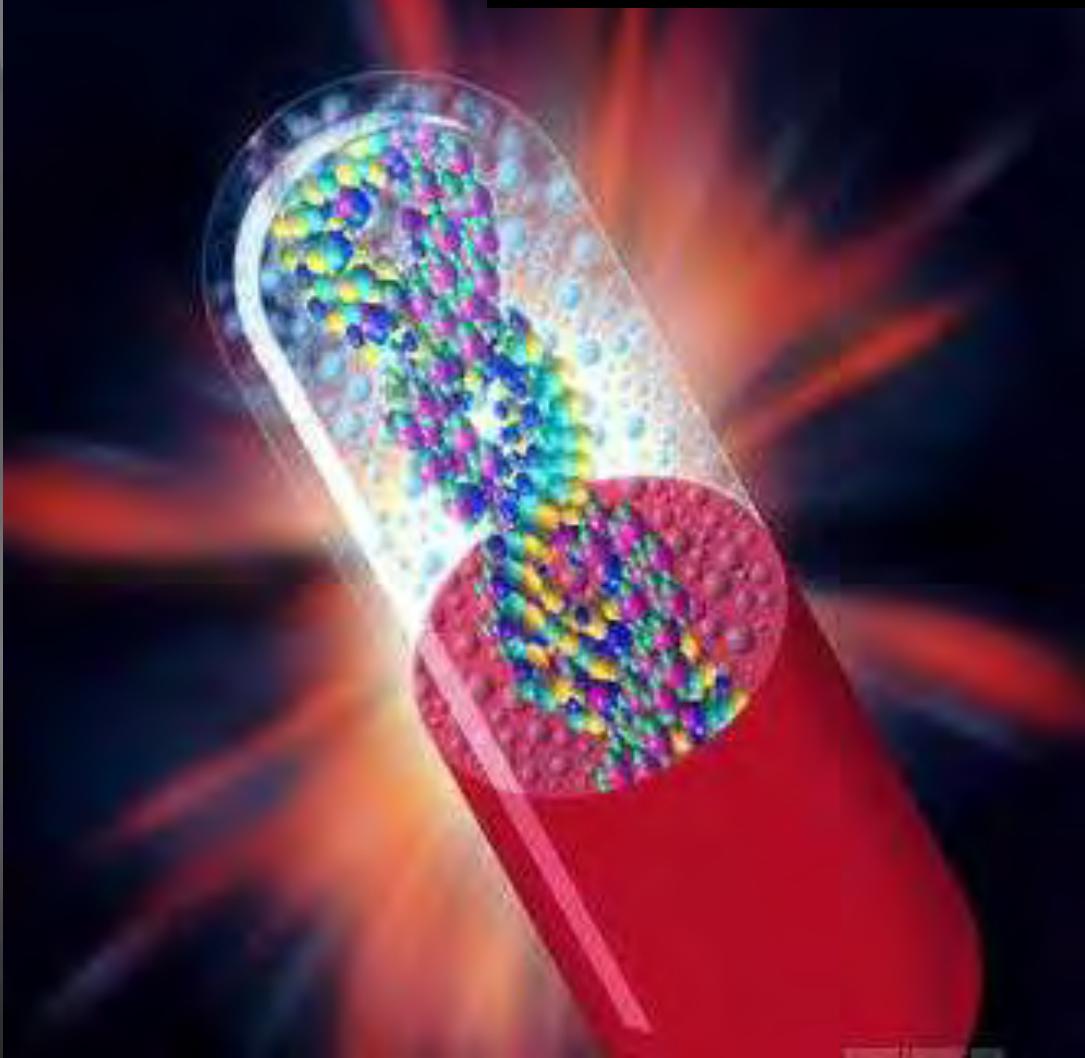


Interaction of CYP2D6 and APOE in the Pharmacogenetics of Alzheimer's Disease

Influence of APOE Genotypes on CYP2D6-Related Extensive (EM), Intermediate (IM) and Poor Metabolizers (PM)

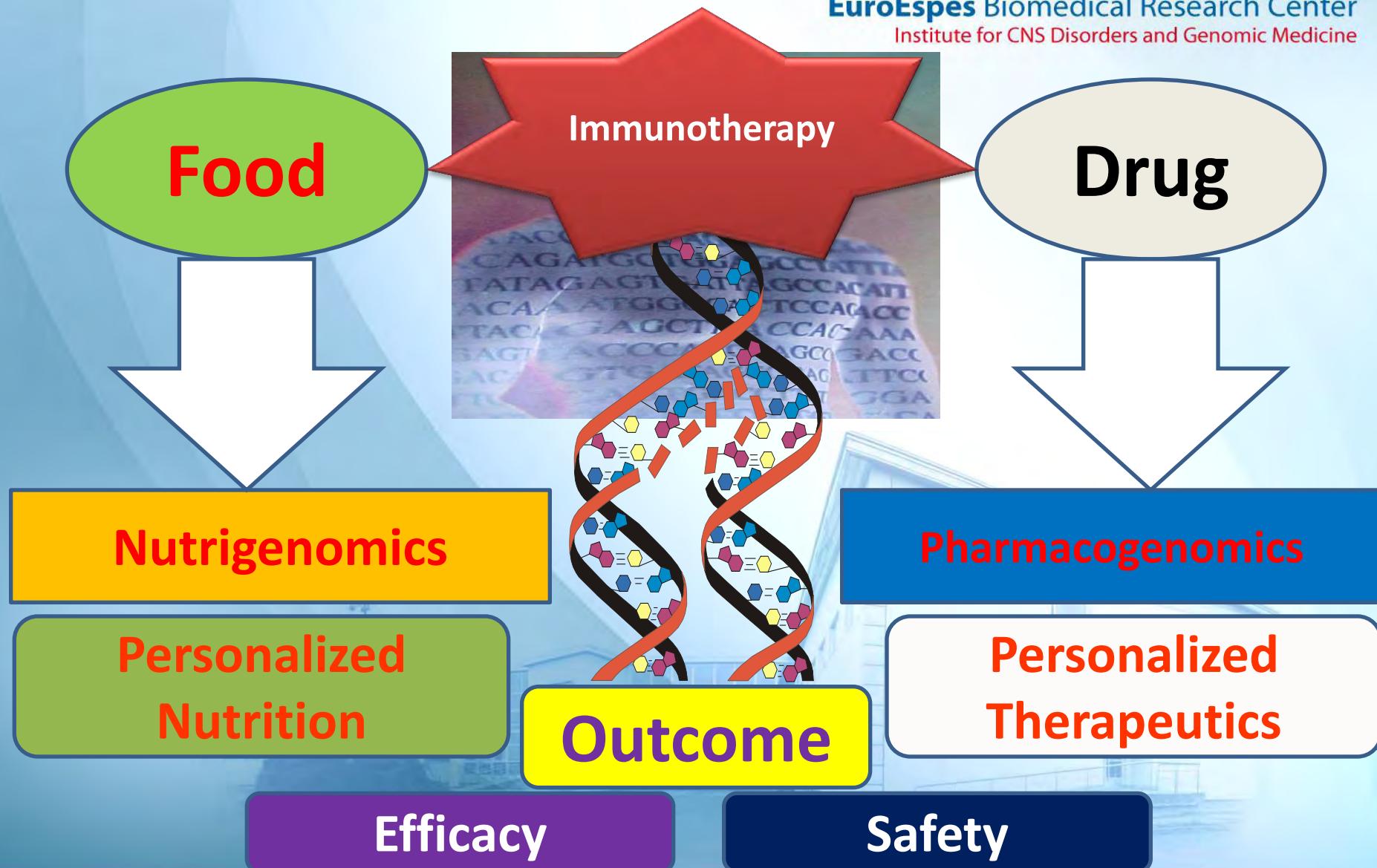


Farmacogenómica

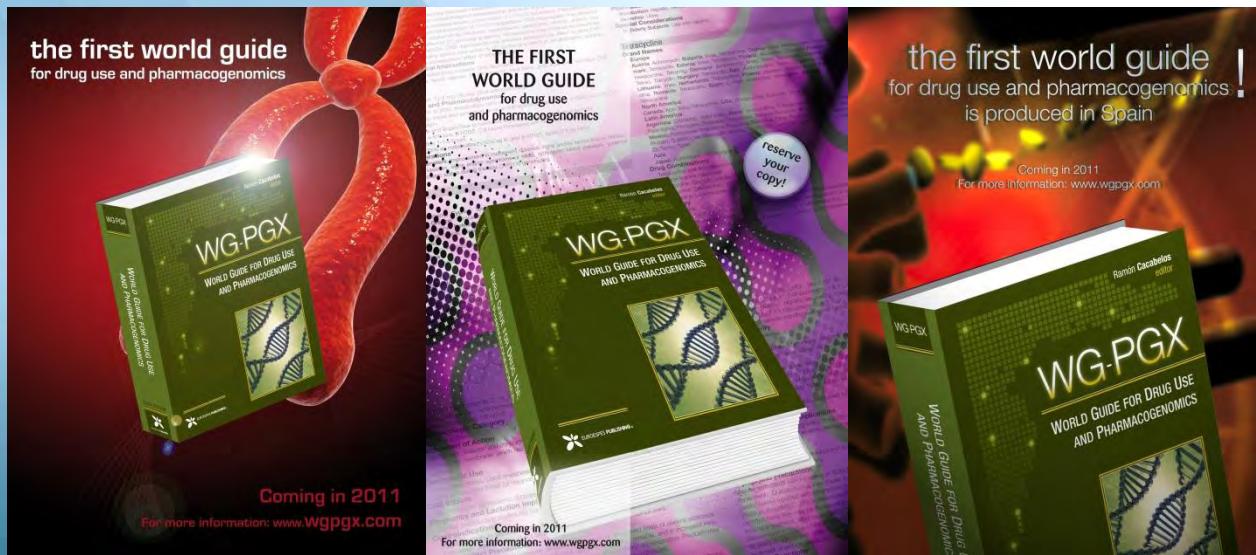


Fármacos
a la Carta





World Guide for Drug Use and Pharmacogenomics



Gracias

