ICC

"The neuroimmunmodulation theory of Alzheimer´s disease

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PRESENTED TO: III IBEROAMERICAN CONGRESS ON NEUROIMMUNOMODULATION, BUENOS AIRES ARGENTINA

ICC

Presentation Route

“The neuroimmunmodulation hypothesis of Alzheimer´s disease (AD)”

1. Alzheimer´s disease: a major puzzle to Medicine
2. The multidisciplinary approach to AD
3. Major hypotheses in AD
4. Tau as a common final pathway in AD pathogenesis
5. AD as an autotoxic disease
6. The damage signals hypothesis of AD
7. Cytokines and signaling pathways in AD

Why is AD a Public Health Problem?

Increasing Prevalence

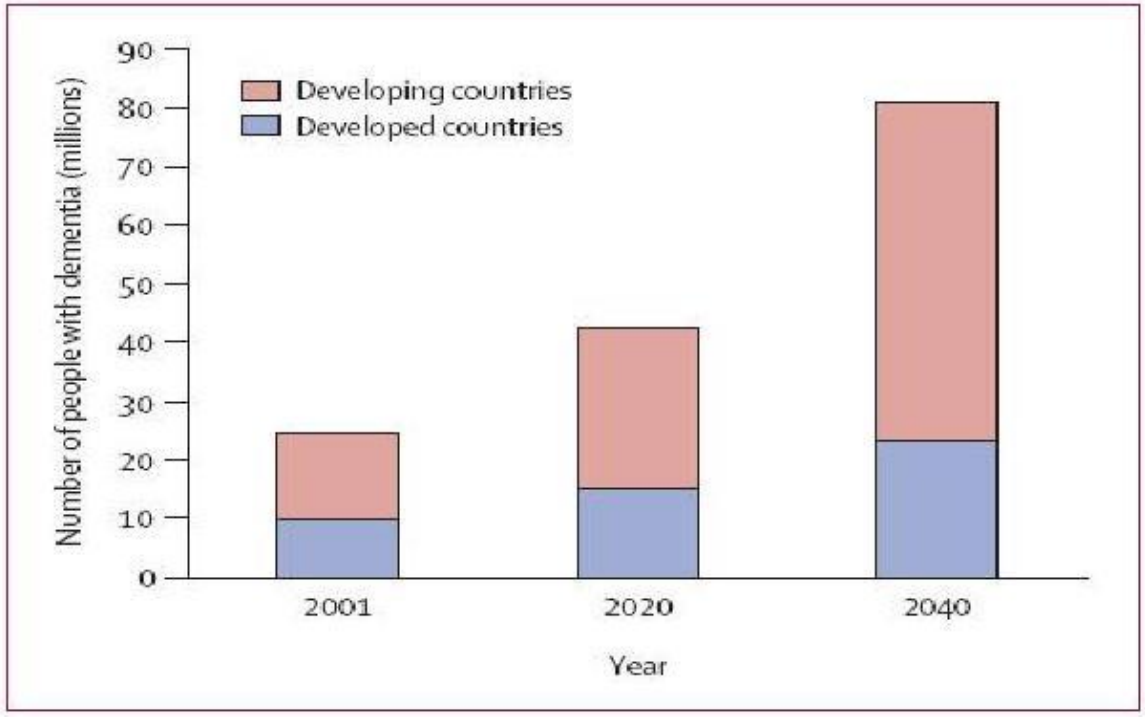


Figure 2: Number of people with dementia in developed and developing countries

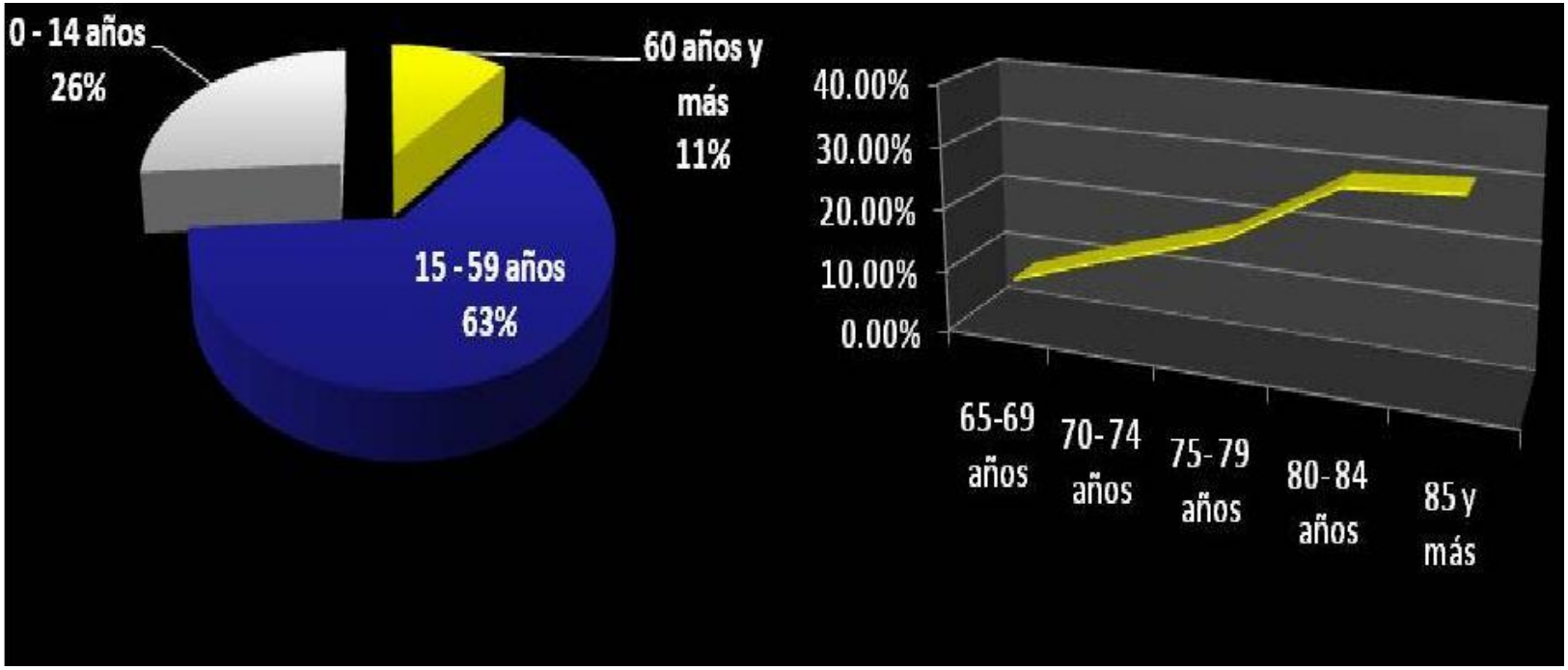
2/3 of dementia patients live in developing and underdeveloped countries

Ferri et al., 2005
Kalaria et al., 2008

Alzheimer's Disease is a major Puzzle to Public Health, Medicine and Society.

Age distribution of the Chilean population

Prevalence of AD among Chilean population

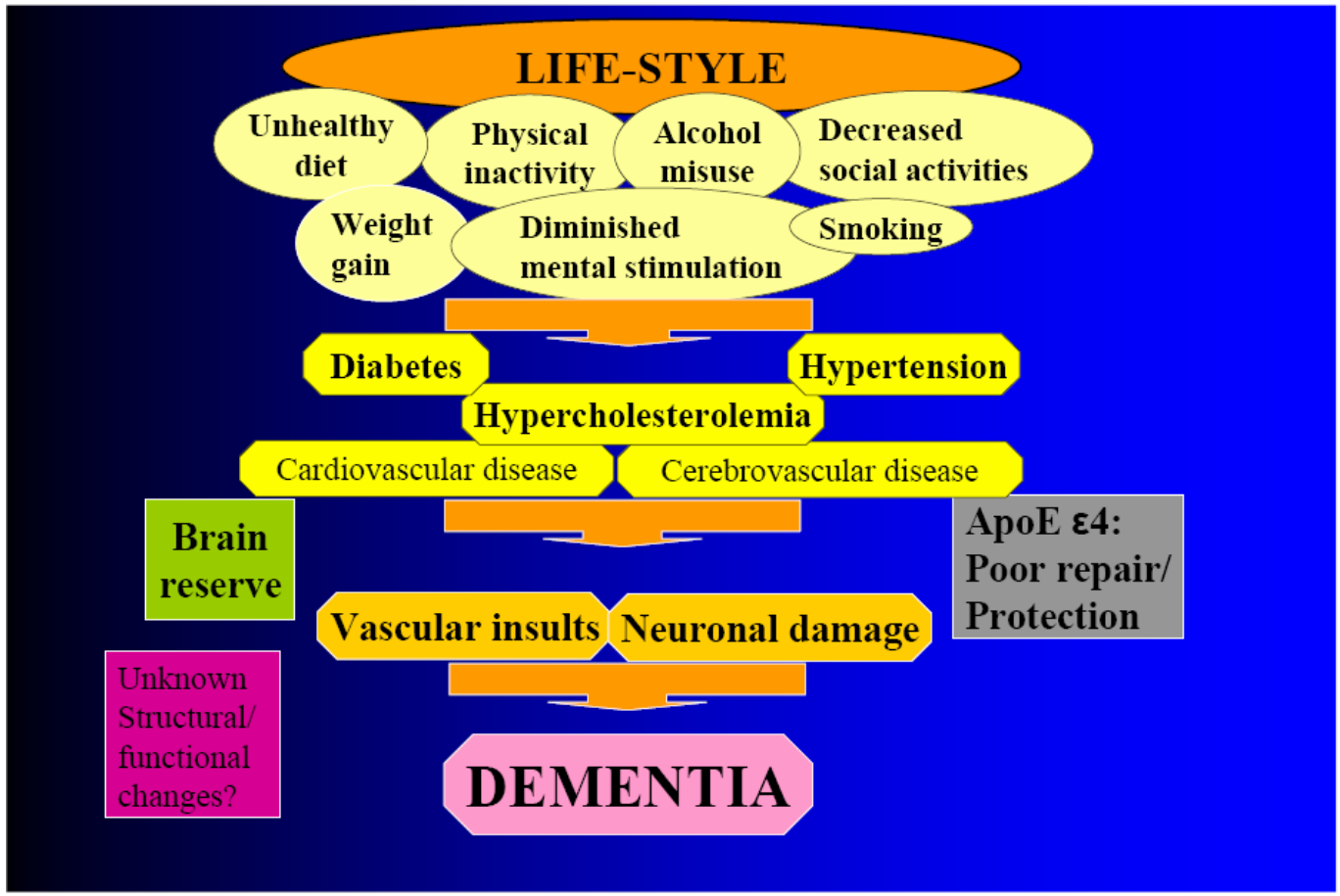


Chile: over 175,000 people with AD (INE National Census 2002; Quiroga, 1995)

(Ferri et al., 2005)

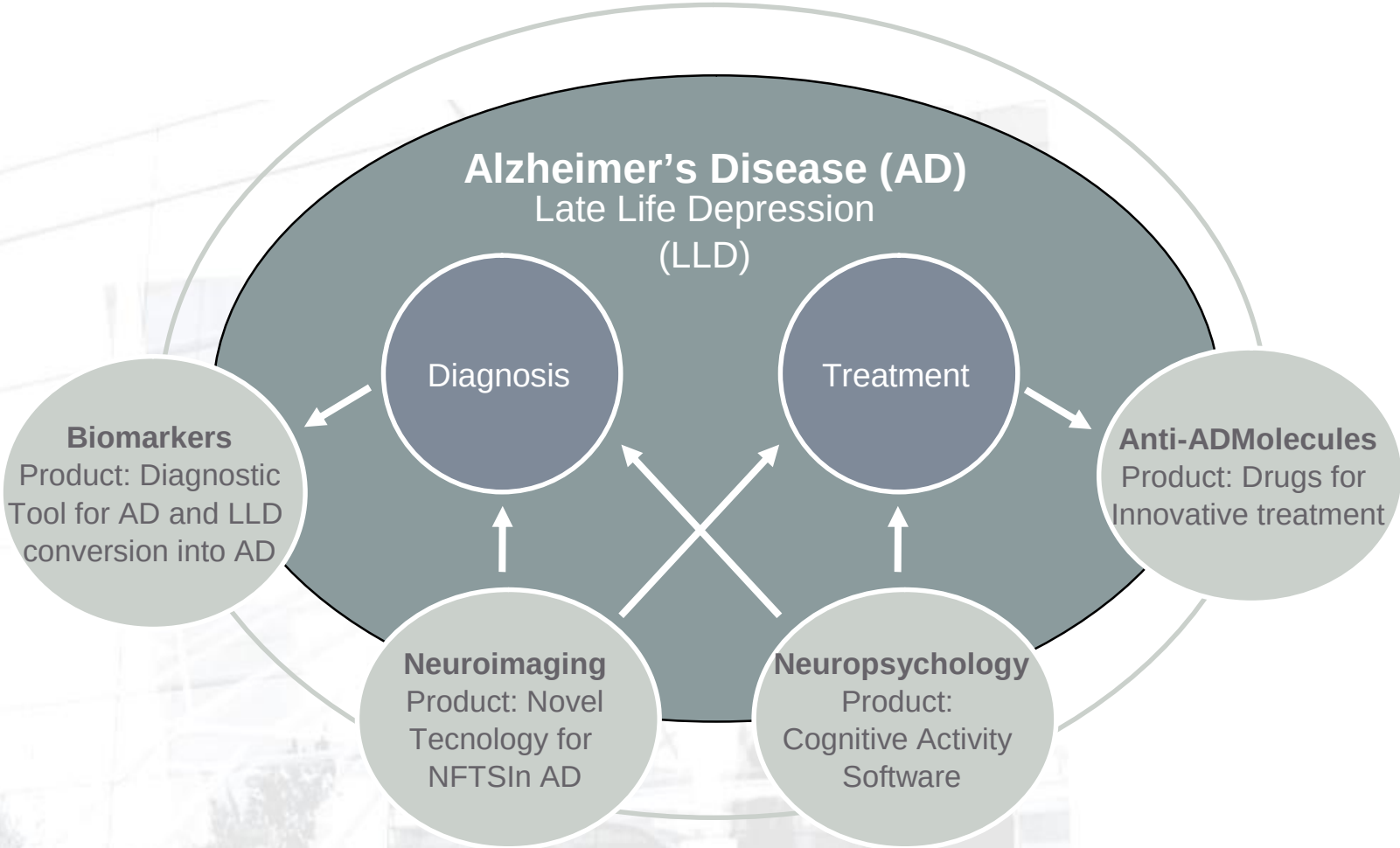
MAIN CHALLENGES IN AD RESEARCH

PREVENTION, DIAGNOSIS AND TREATMENT

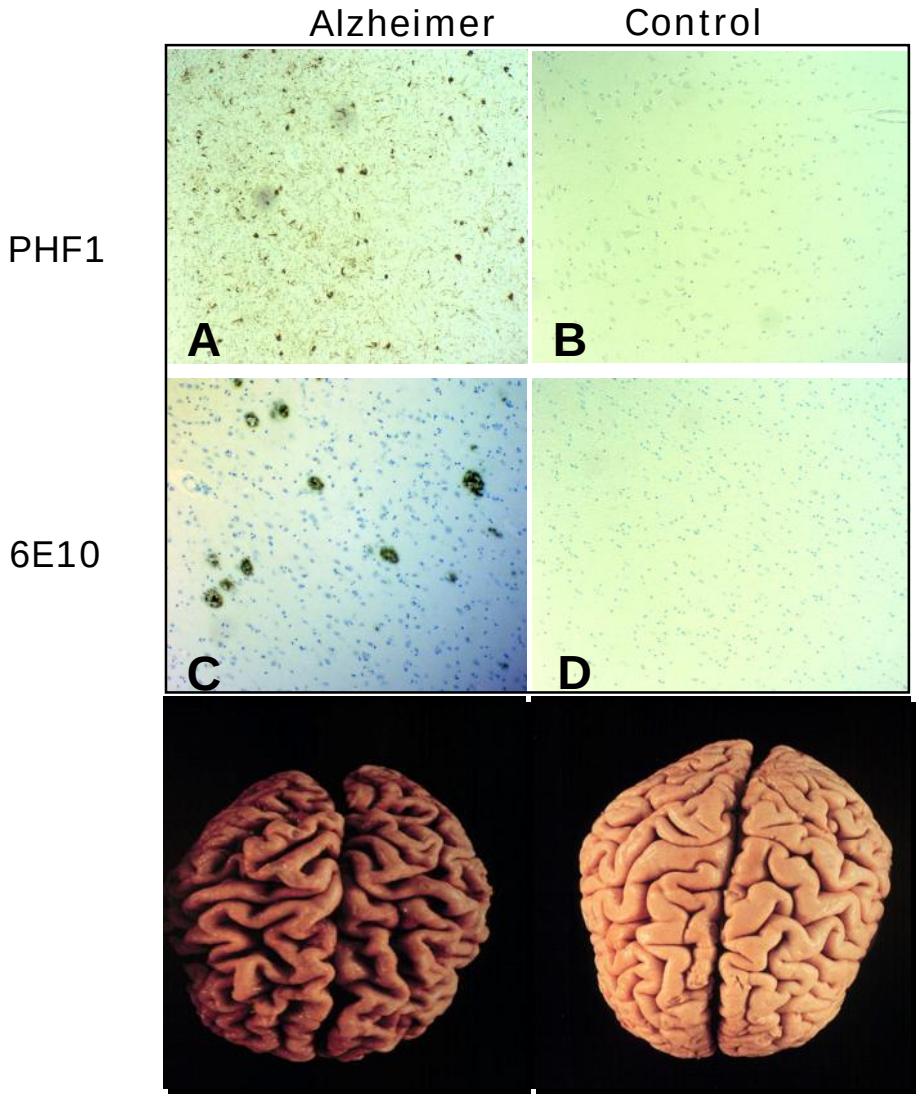


THE LABORATORY OF CELLULAR & MOLECULAR NEUROSCIENCES

Our Laboratory tackles AD with a multidisciplinary approach

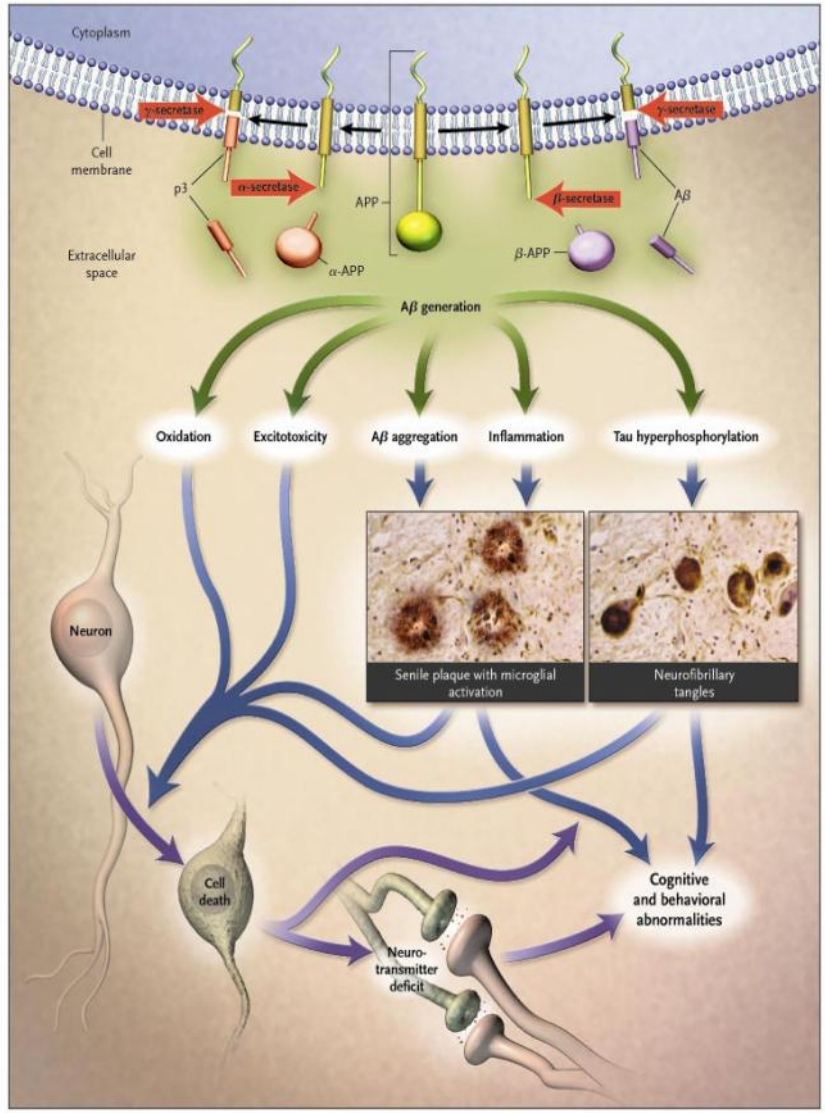


NEUROFIBRILLARY TANGLES: MAJOR PATHOGNOMONIC LESION IN ALZHEIMER´S DISEASE (AD)



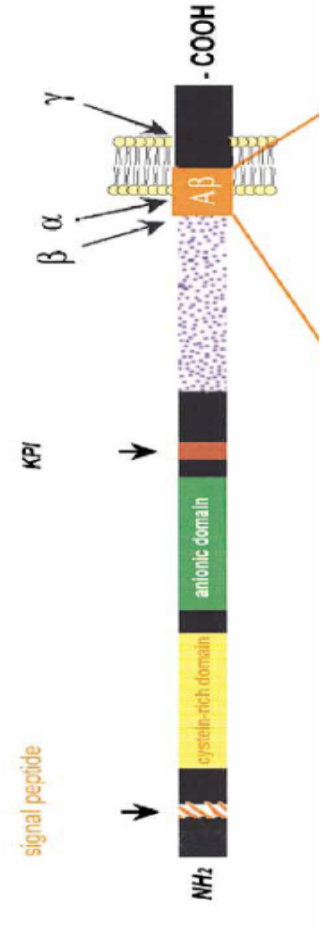
The ‘amyloid cascade’ hypothesis

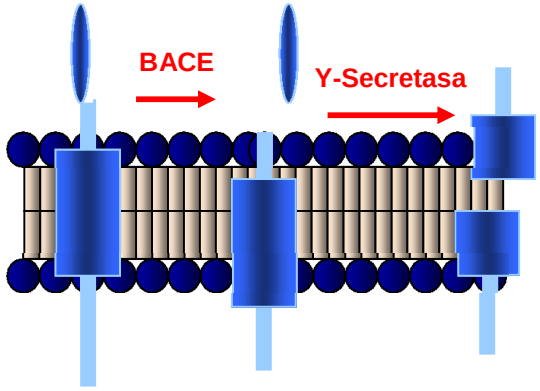
Conceptualized as resulting from the generation of the beta-amyloid (A/β) peptide from the amyloid precursor protein (APP), through multiple secondary steps, to cell death. **It was the foundation for most (but not all) emerging options for the treatment of Alzheimer's disease.**



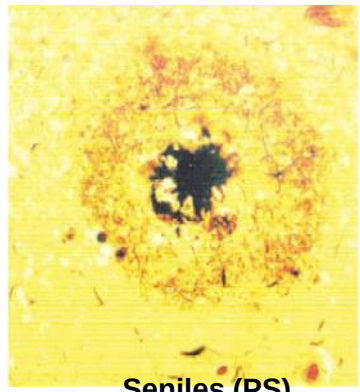
- **Reproduced from: Cummings, J (2004) NEJM 351:56-67**

Senile Plaques Formation





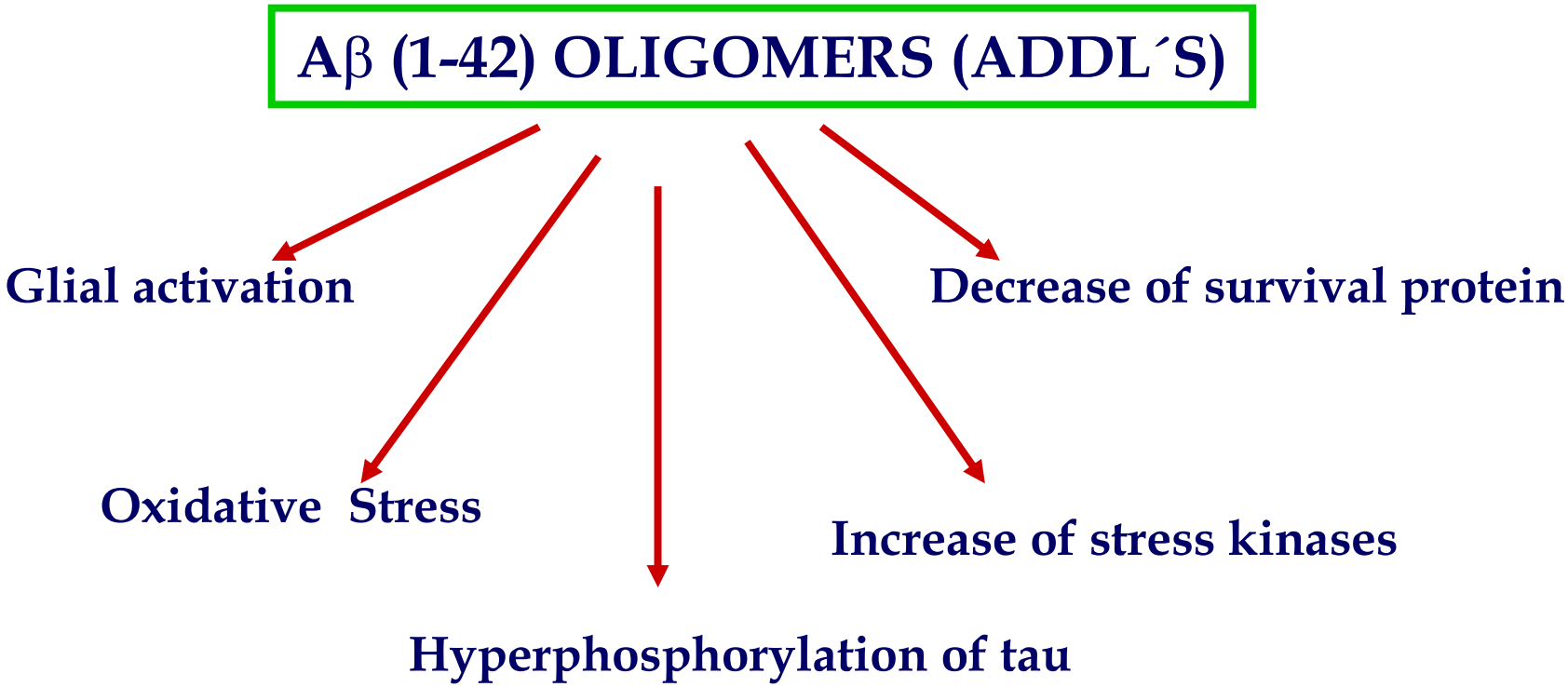
AMYLOIDOGENIC PROCESSING OF APP
To form Aβ1-40 y Aβ1-42*



Seniles (PS)
Agregación de péptidos Aβ

Amyloid precursor protein (APP) generating Aβ

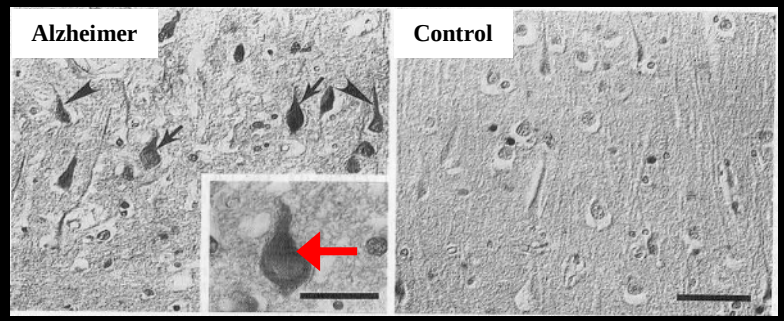
Maccioni RB et al, Arch Med Res, 2001



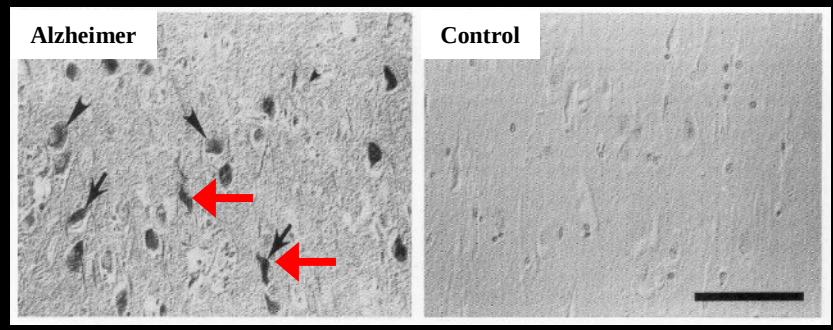
- **Insulin-like growth factor-1 receptor**
- **Erythropoietin**
- **Estrogen**
- **Interleukin-3 (Zambrano et al.)**

These factors induce an increase **in survival proteins** → These factors protect against β-amyloid-induced neurotoxicity

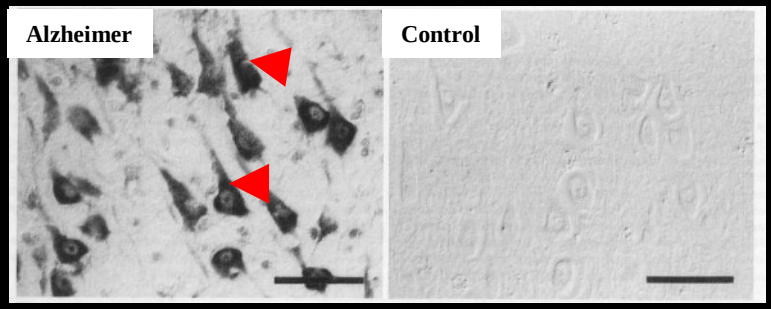
Oxidative damage hypothesis of Perry and Smith



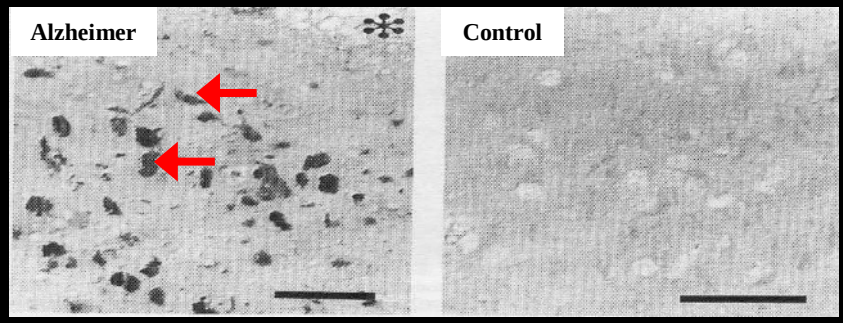
Lipid Peroxidation/Protein Adduction (4-HNE)



Protein Oxidation (Free Carbonyl Groups)

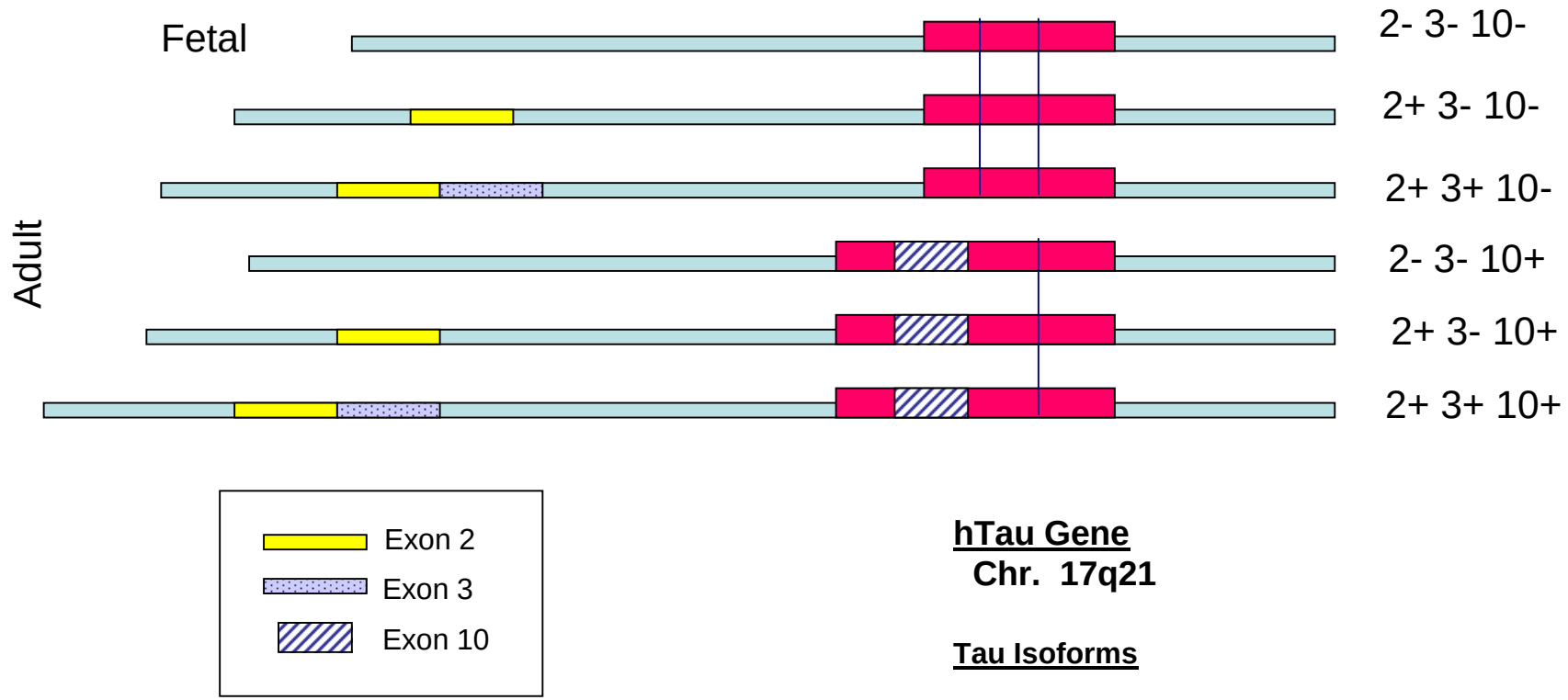


Nucleic Acids (8-OH-Guanosine)



Glycoxidation (Carboxymethyllysine)

There are six isoforms of human tau produced by alternative splicing of a single gene

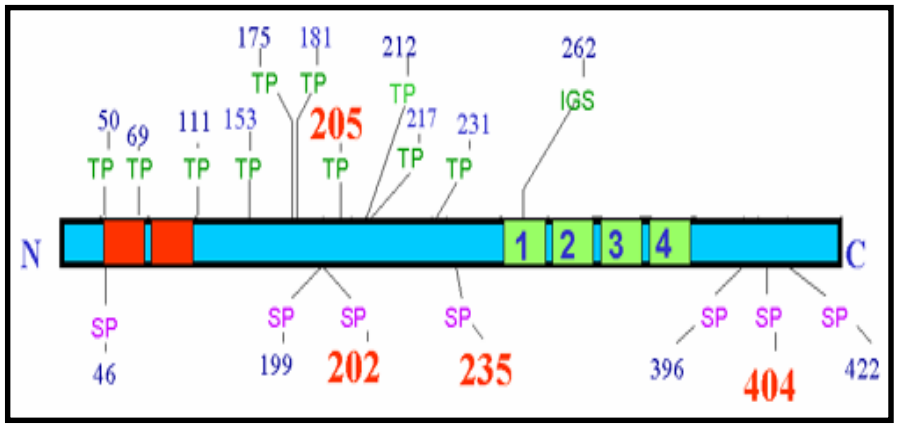


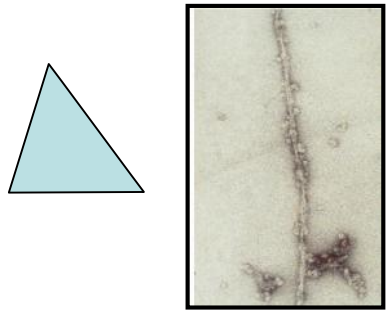
hTau Gene
Chr. 17q21

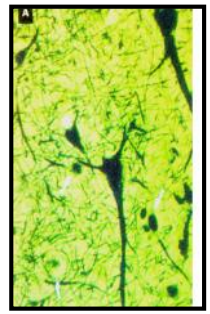
Tau Isoforms

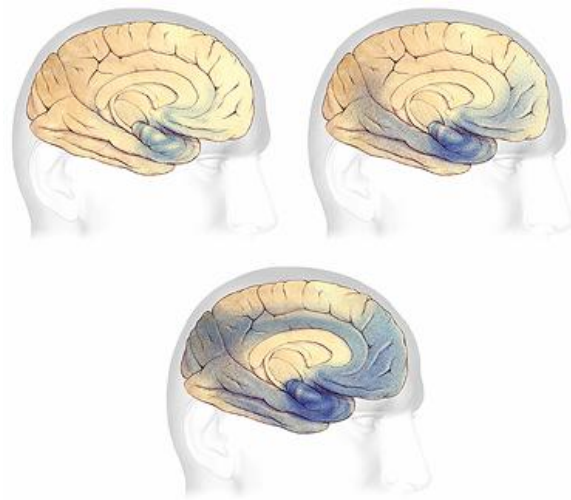
45-65 kD (352-441)

IN THE CONTEXT OF AD PATHOGENESIS



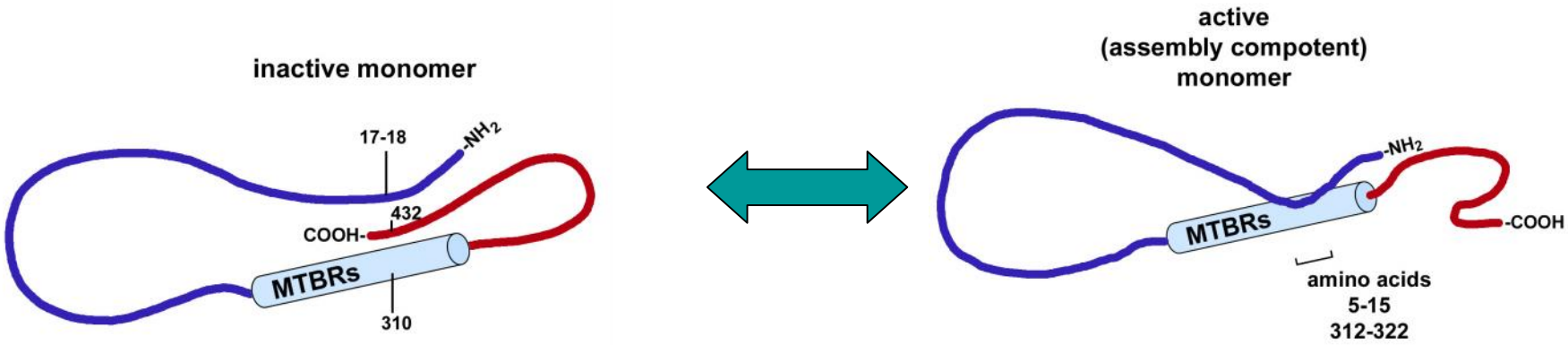






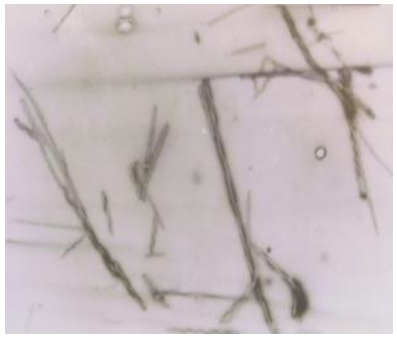
(Maccioni et al, 2001, Guillozet et al, 2003)

PATHOLOGICAL FOLDING OF TAU TO FORM PHF´s



TAU MONOMER

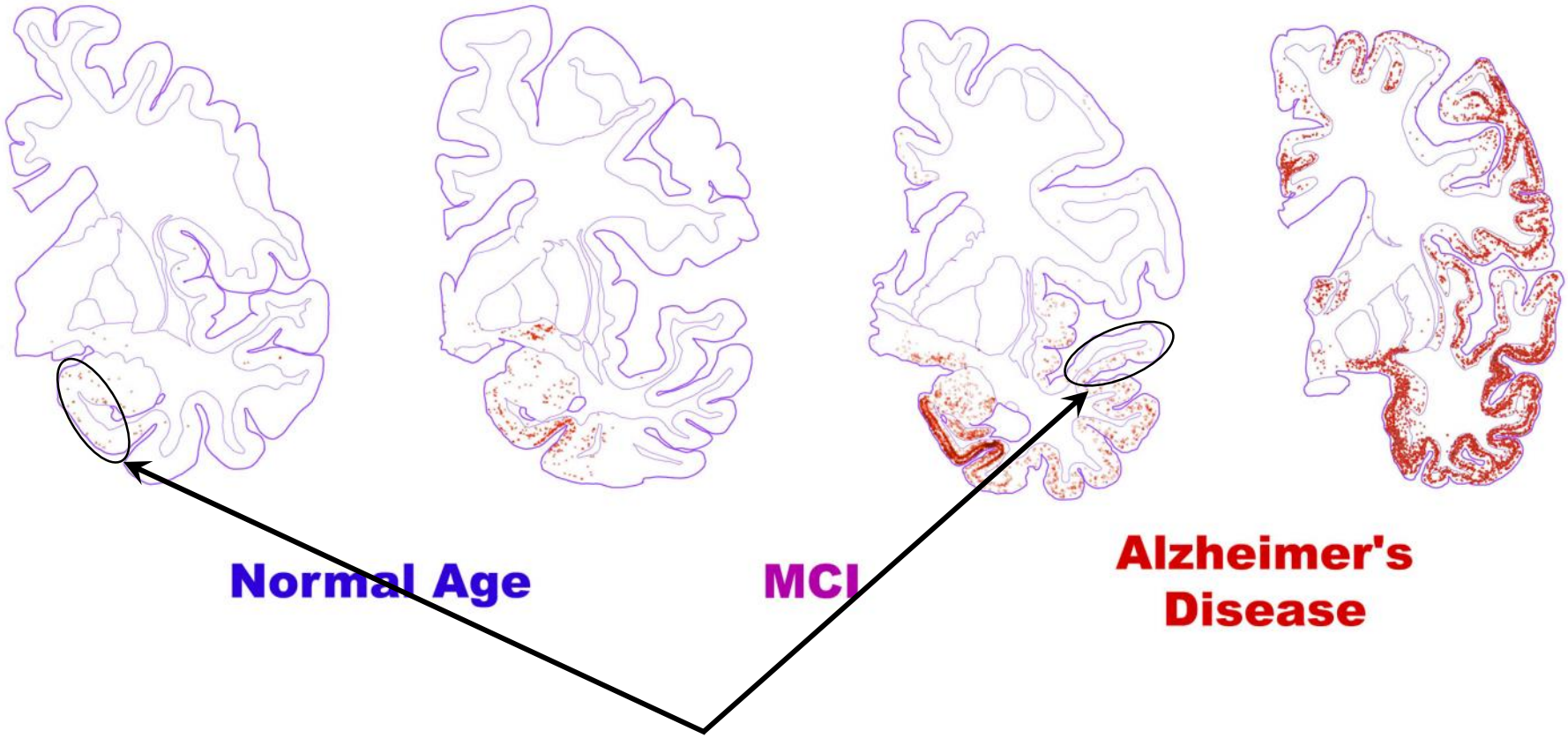
Epítope of MC-1 Ab



POLYMERS

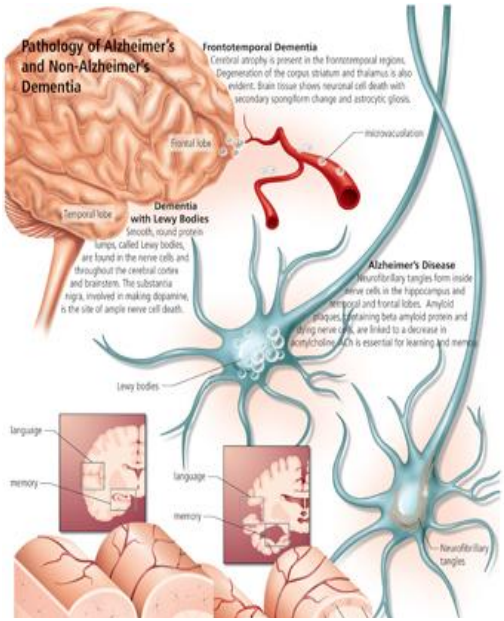
Paired helical filaments (PHFs)

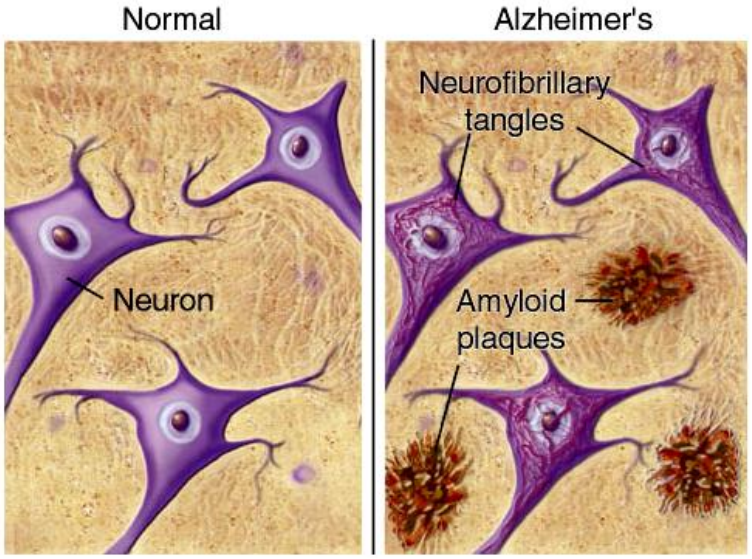
Distribution of Neurofibrillary Tangles



SAME AGE

Tauoapathies





PHF

Polymers of modified, or cleaved tau protein

↓

NFTs

↓

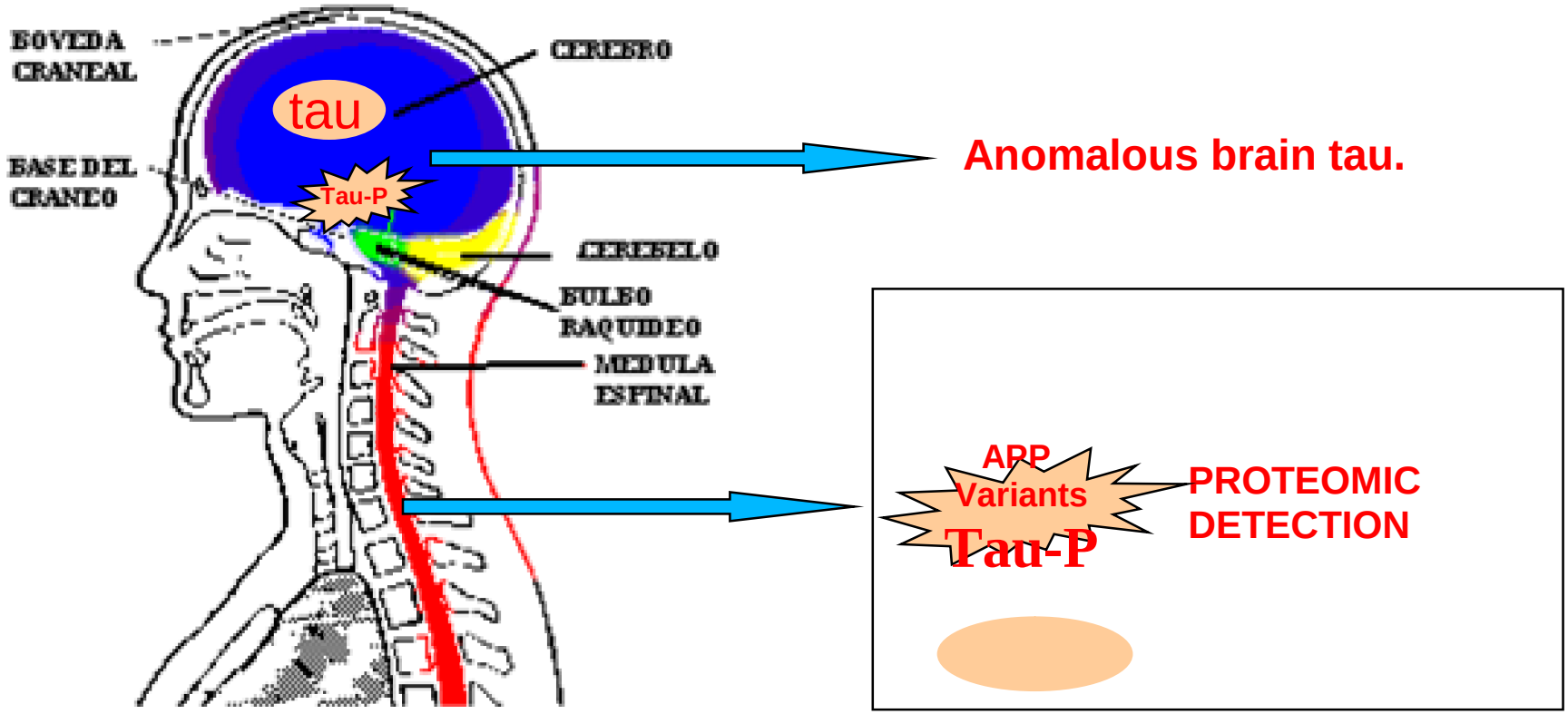
Tauopathies

Alzheimer´s disease
Pick Disease
DFTP-17
Down syndrome
Progressive Supranuclear Palsy (PSP)

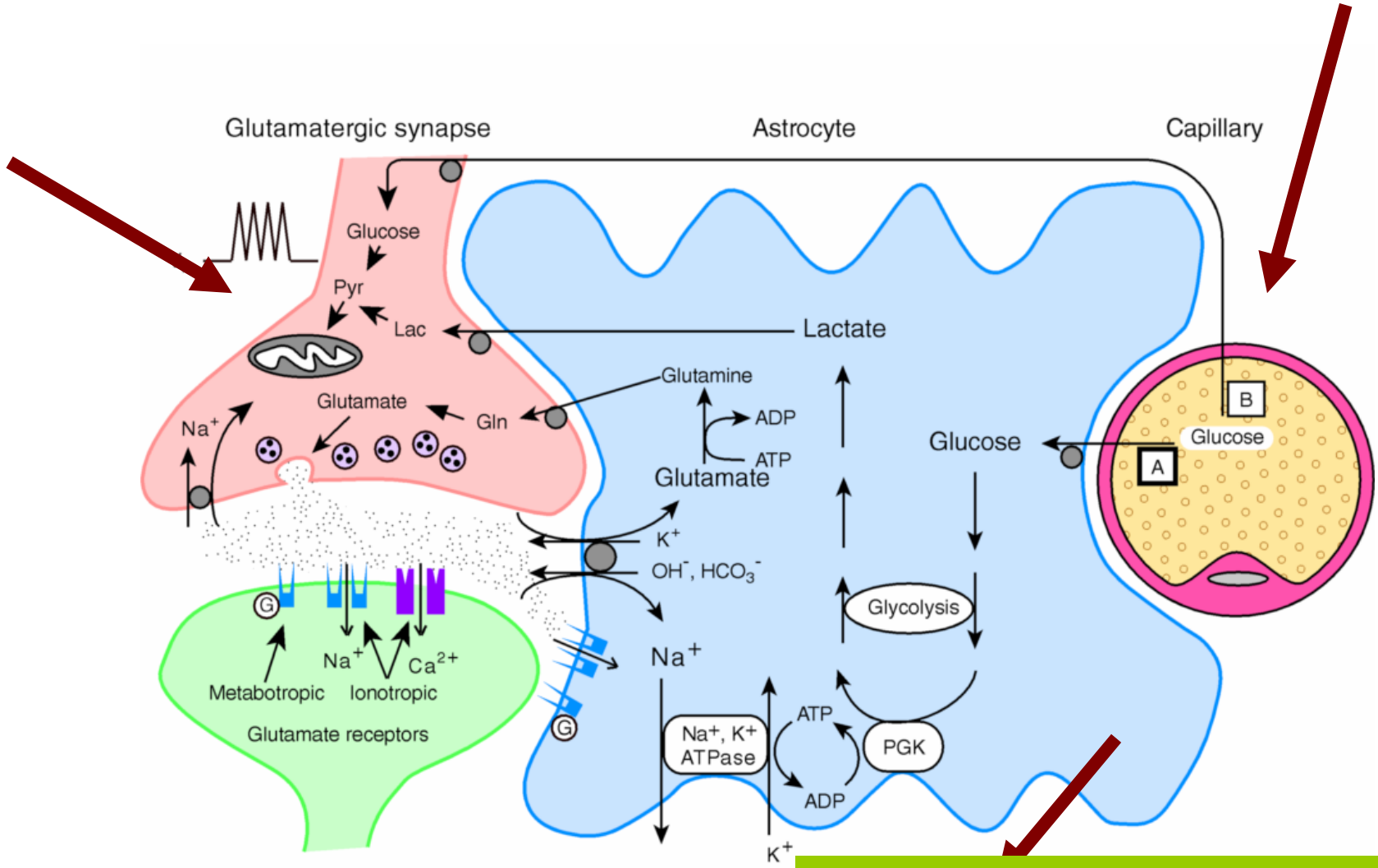
Bridge Between Basic and Clinical Research.

TAU BIOMARKERS IN CSF

Maccioni et al. (2006) Neurobiol Aging.



THE NEURAL UNIT: glia/neurons/vessels



PROINFLAMMATORY MEDIATORS

Microglia are normally beneficial but are toxic when overactive

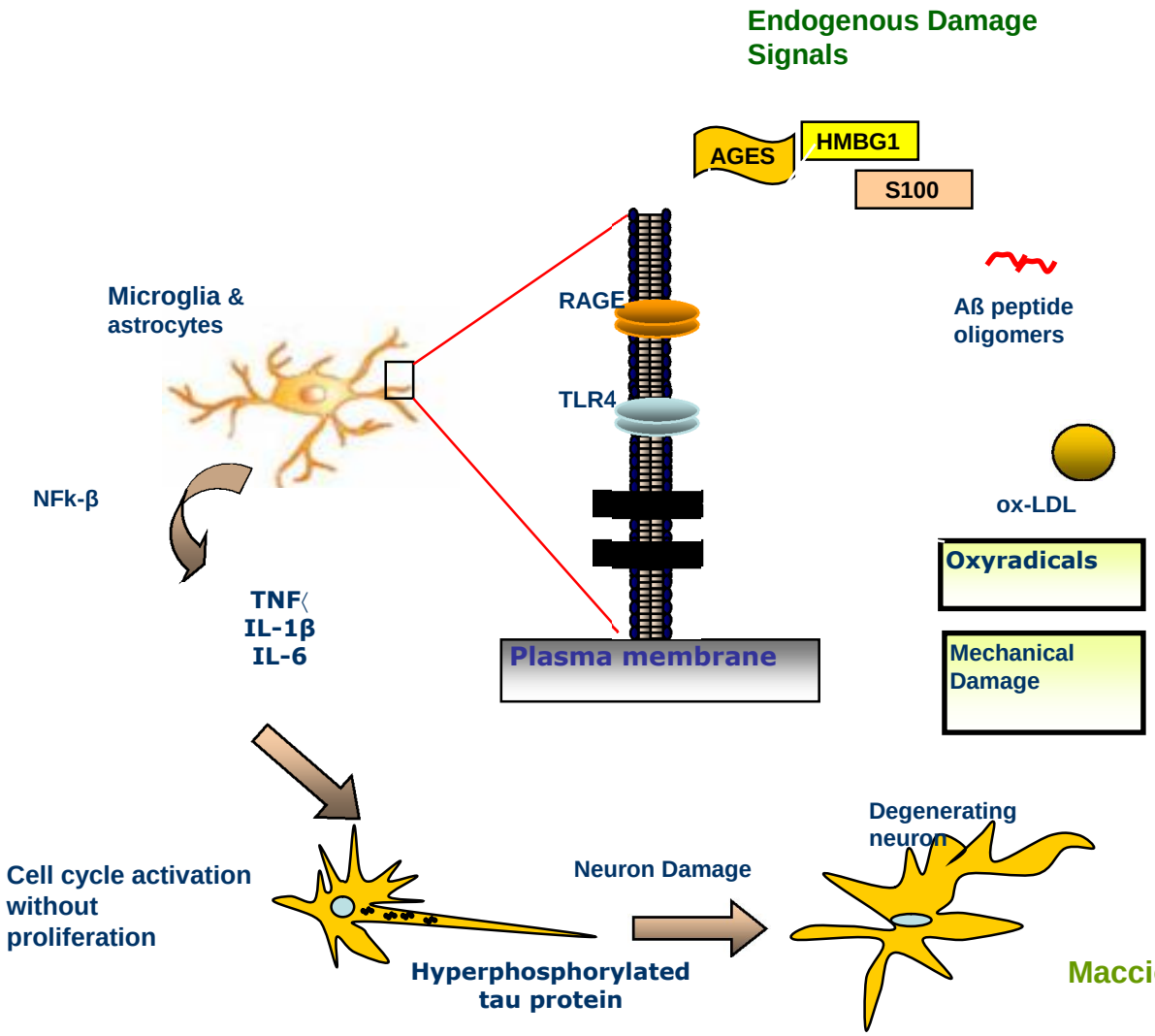
- **Helpful actions include phagocytosis and killing pathogens**

- **Harmful actions include excess production of oxygen free radicals, complement proteins, inflammatory cytokines, prostaglandins, glutamate and many as yet unidentified products**

Which signals are responsible for AD pathogenesis?

THE NEED OF A UNIFYING HYPOTHESIS.

Testing Neuroimmunomodulation hypothesis of AD. Search for Treatment Avenues.



External Factors

Deleterious

- Head injury
- High fat Intake
- Deficiency in B vitamins
- Infections
- Iron Overload

Protective

- Statins
- NSAIDs
- Long-term exposure to cholinergic agonists (?)

Maccioni et al Ann NY Acad Sci 2009

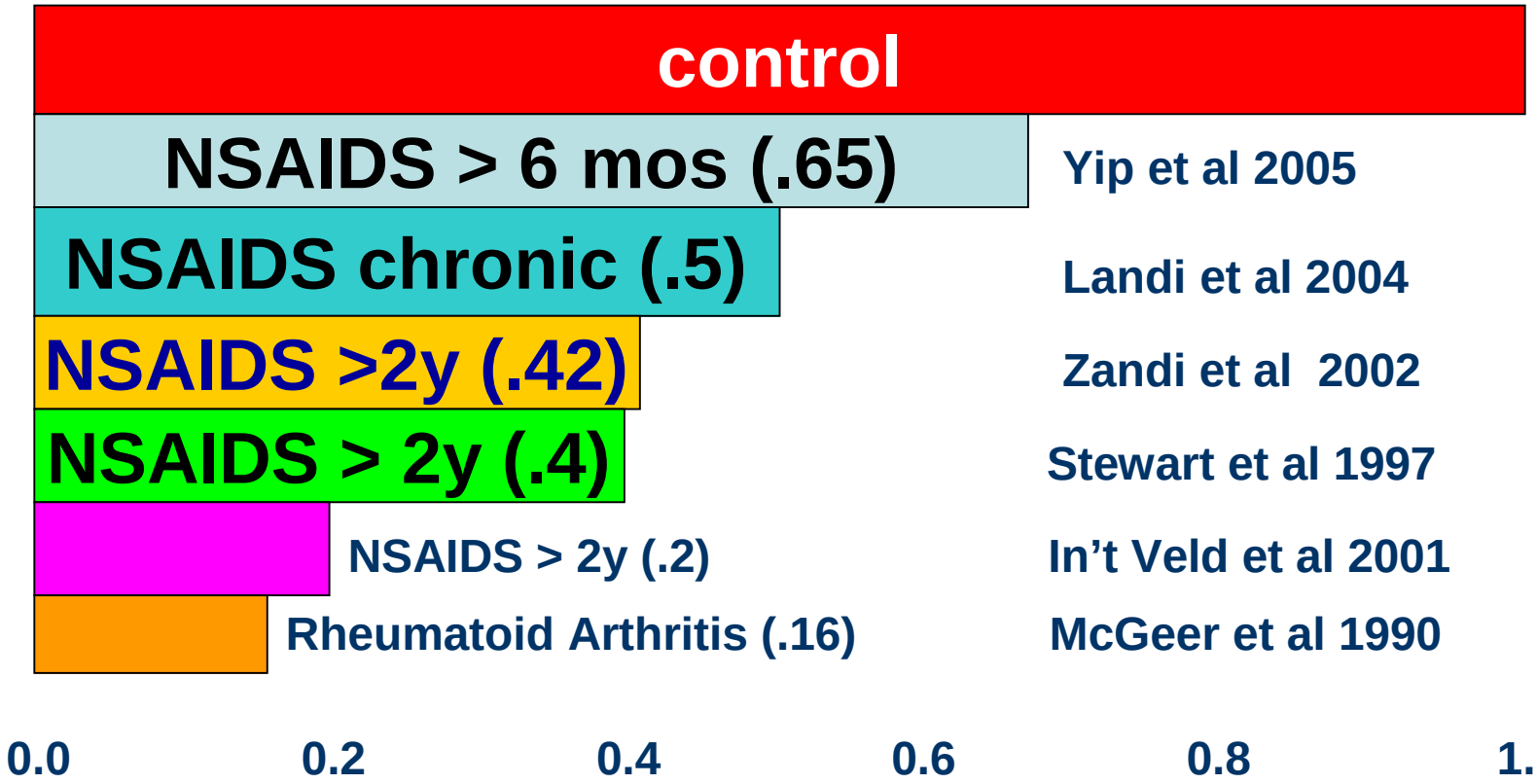
Autotoxic diseases are different from autoimmune diseases

- **Autoimmune diseases involve the adaptive immune system. They are aggressive and strike the young**

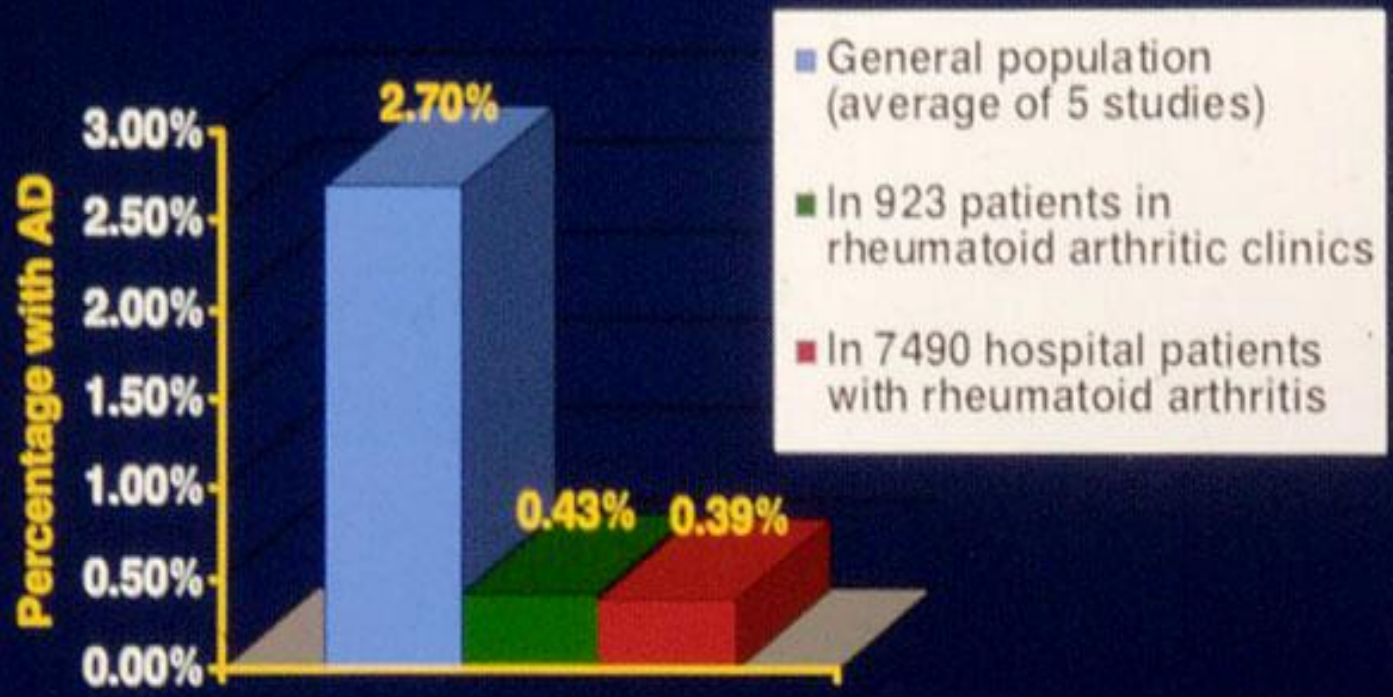
- **Autotoxic disease are less aggressive and strike the elderly. They are much more prevalent than autoimmune diseases**

- **We postulate that the major driving force in AD is neuroinflammation. Activation of the innate immune system**

Treatment with Antiinflammatory drugs reduces the risk of Alzheimer Disease



PREVALENCE OF ALZHEIMER DISEASE IN THE 65 AND OVER AGE GROUP



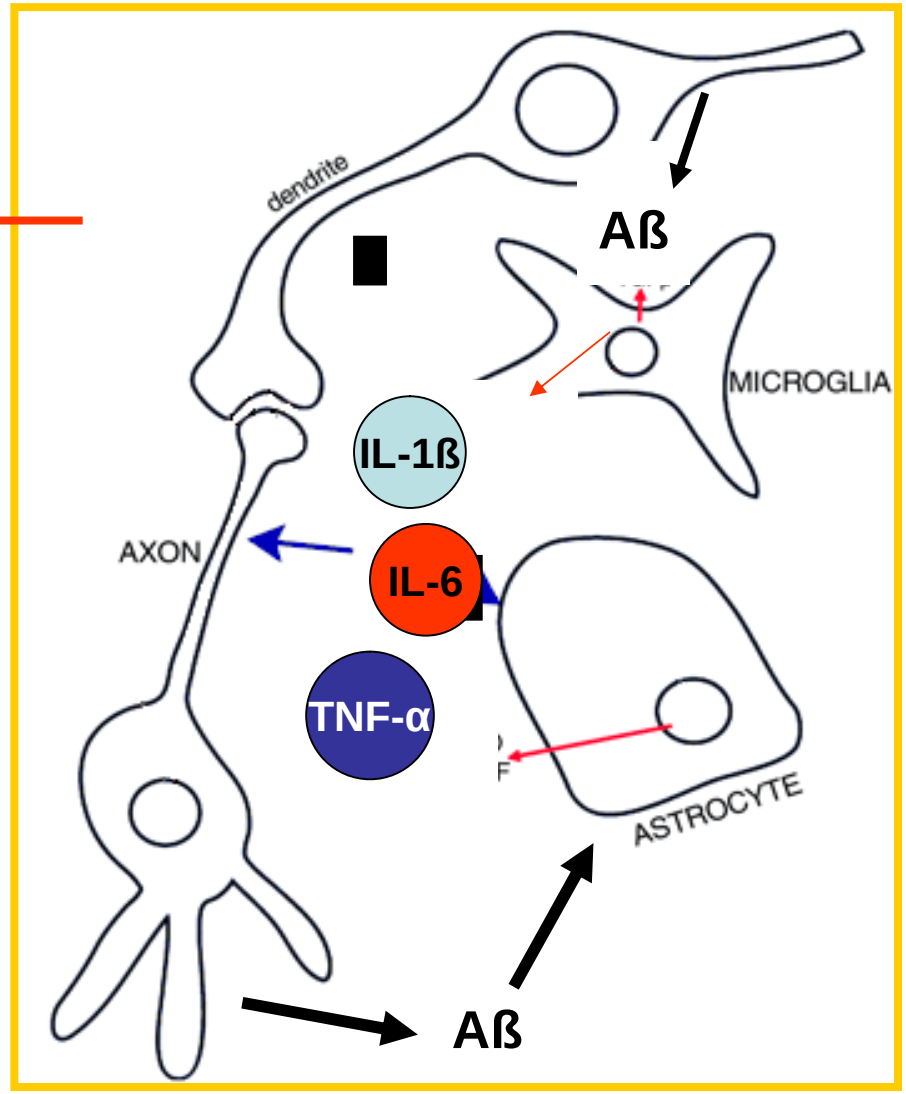
From McGeer et al., Lancet 335:1037, 1991

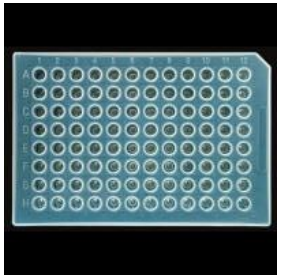
POSITIVE EVENTS

Neurític Growth
Neuronal Differentiation

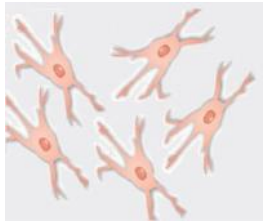
NEGATIVE EVENTS

Apoptosis
Neuronal Dysfunction



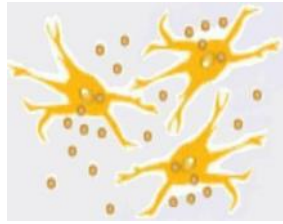


Cultured Microglial cells



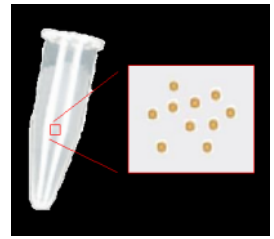
Microglia

H_2O_2



Microglia Over-activated

Interleukins IL-6; IL-1 TNFα

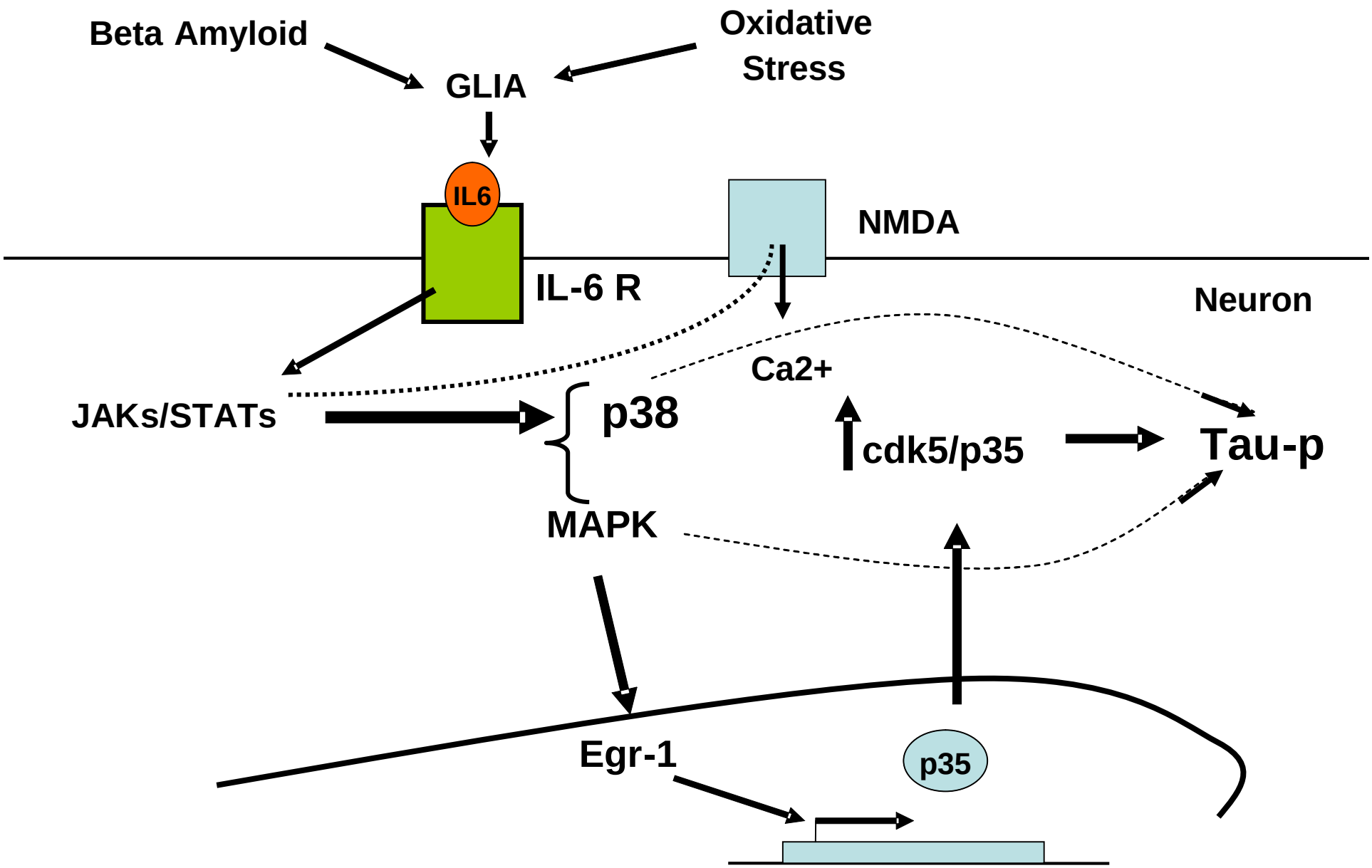


Conditional Media

Cultured Neuron

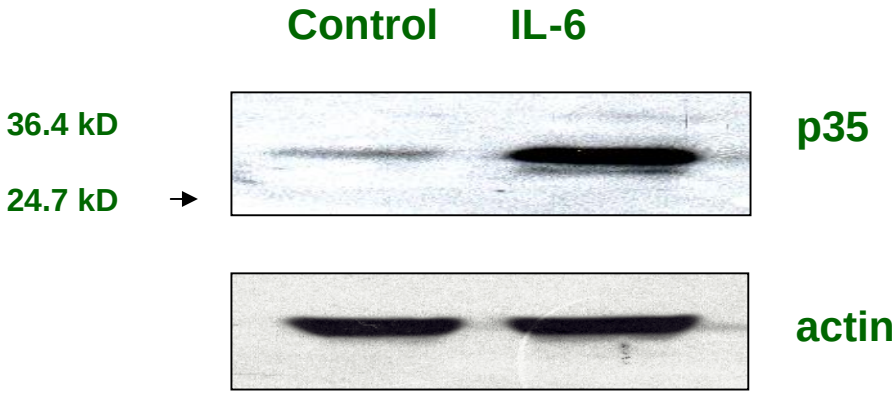
Neurofibrillary degeneration

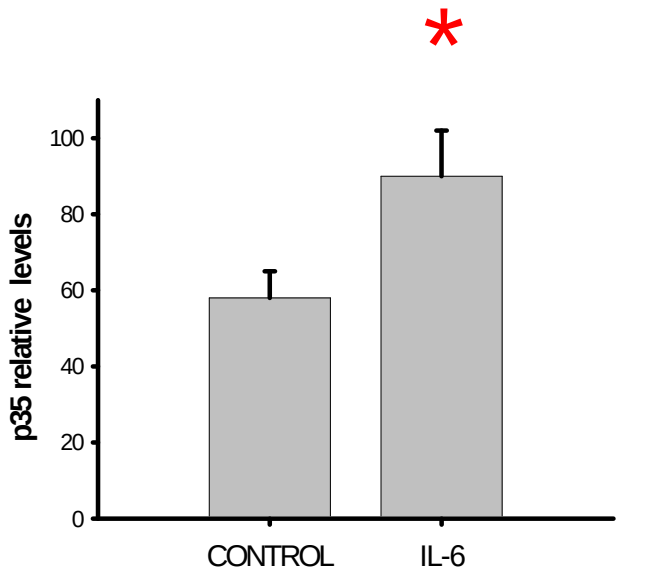
Neurodegenerated cells


Beta Amyloid
Oxidative Stress
GLIA
IL6
NMDA
IL-6 R
Neuron
Ca2+
JAKs/STATs
p38
cdk5/p35
Tau-p
MAPK
Egr-1
p35

IL-6 INDUCES p35 IN RAT HIPPOCAMPAL NEURONS

A





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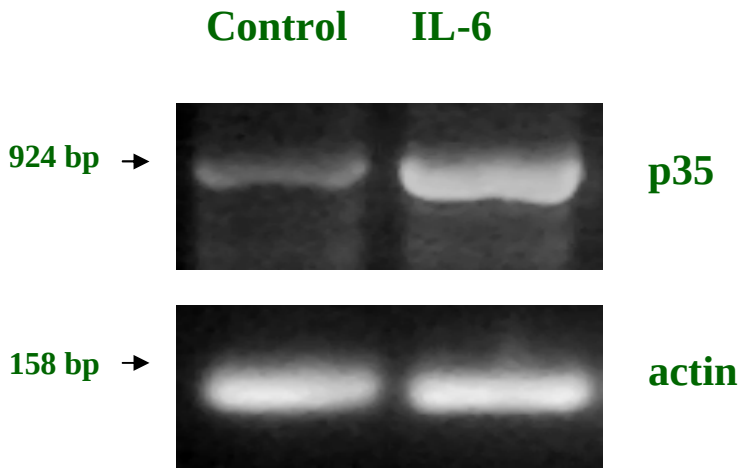
B

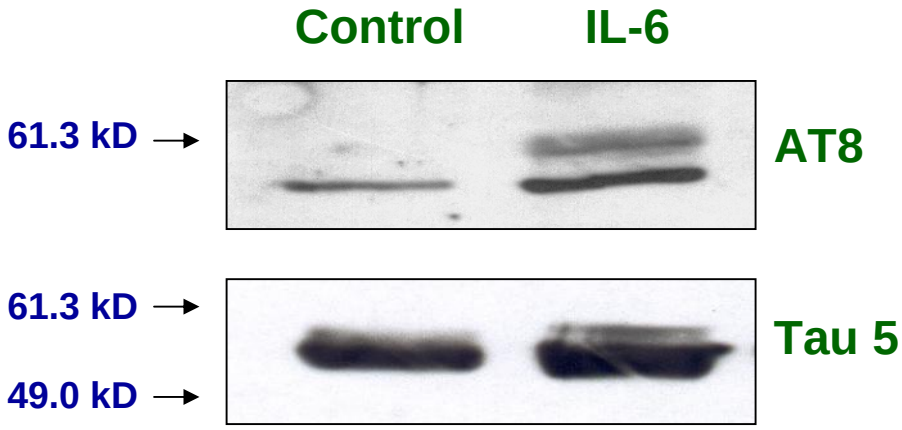


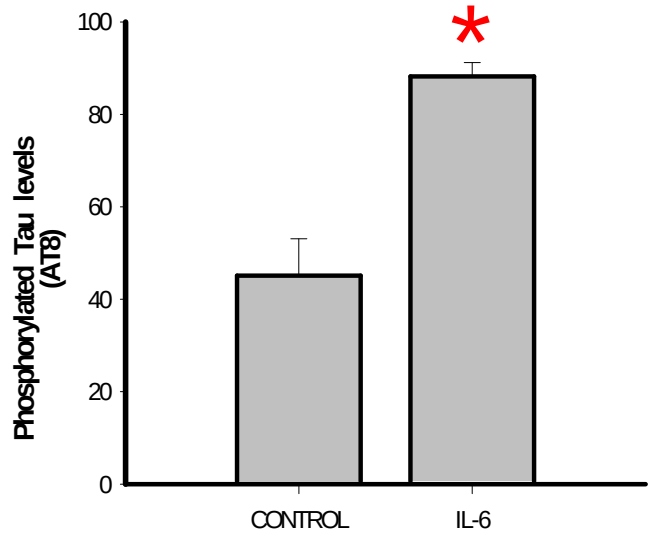
RT-PCR

IL-6 (5ng/ml) x 48h

IL-6 PROMOTES TAU HYPERPHOSPHORYLATION IN AD EPITOPES

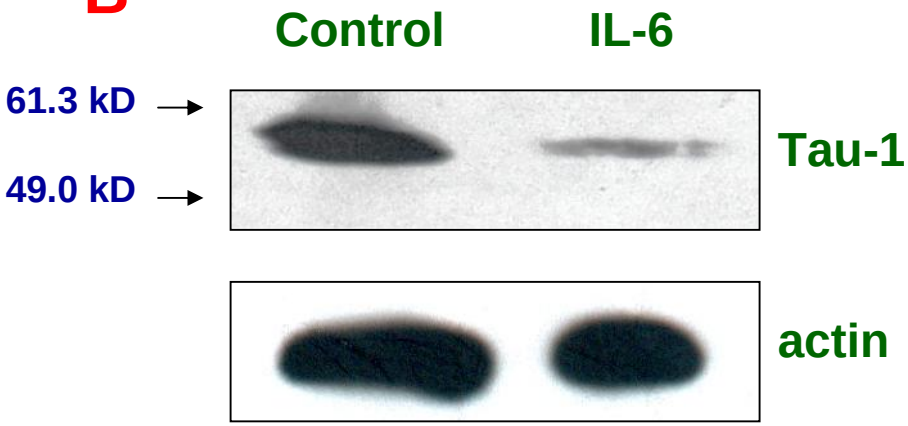
A

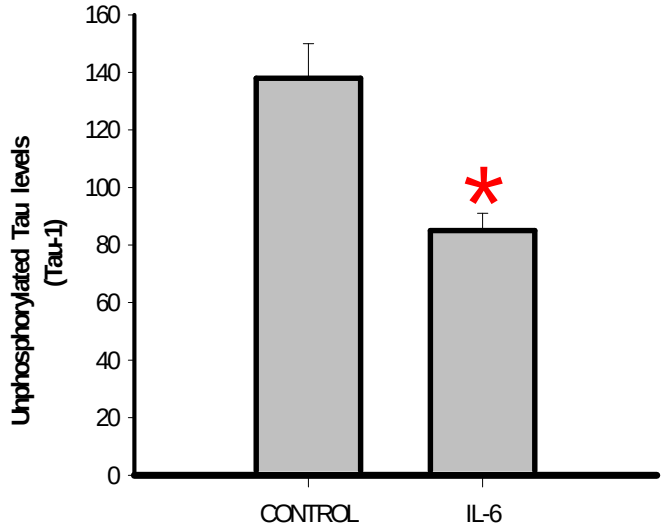




n= 6

B



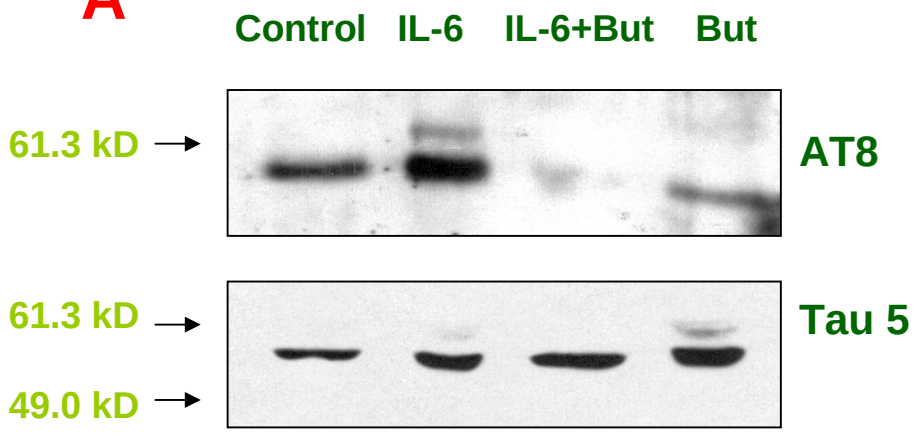


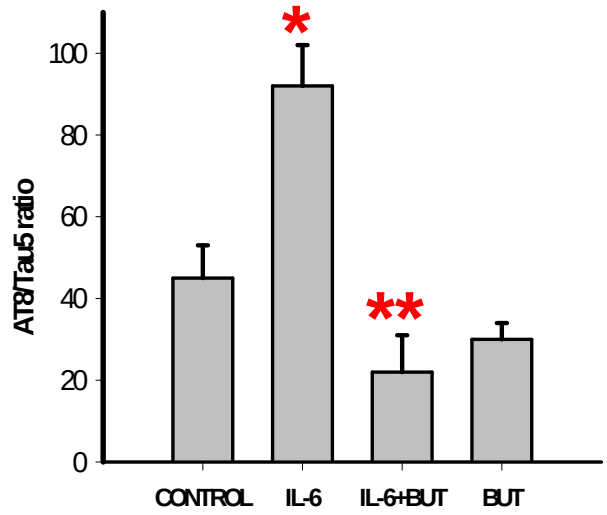
n= 6

IL-6 (5ng/ml) x 48h

IL-6 INDUCED TAU PHOSPHORYLATION IS DEPENDENT ON cdk5/p35

A





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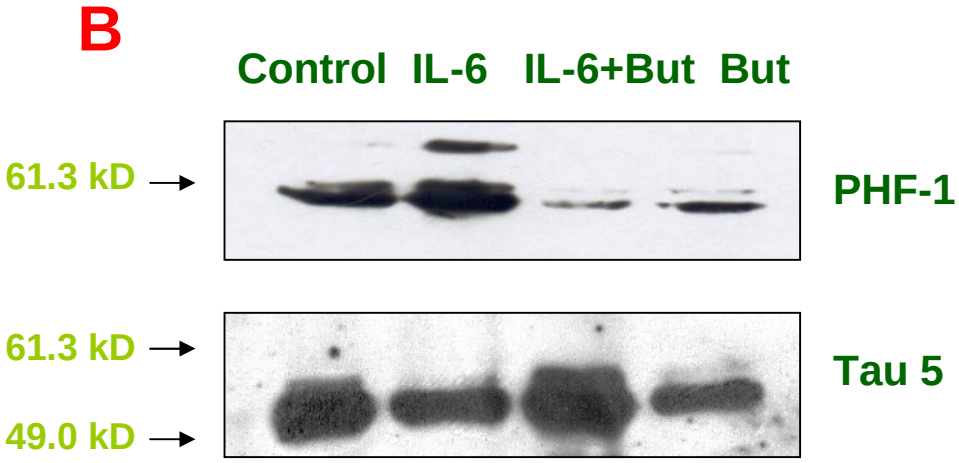
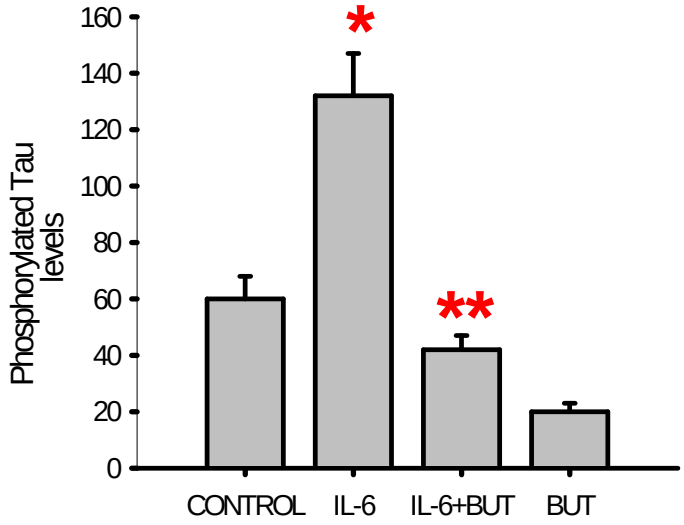
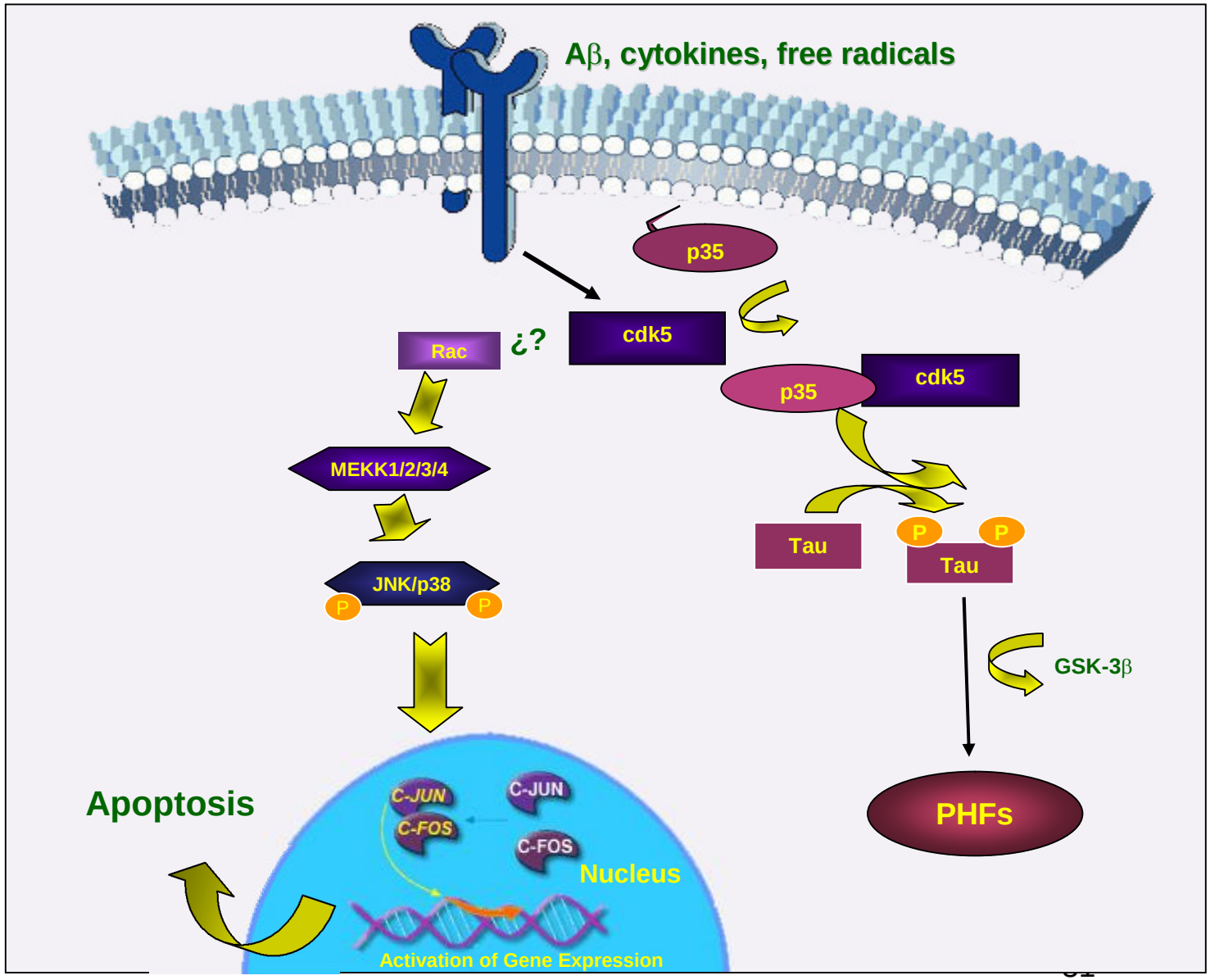




IL-6 (5ng/ml) x 48h **But(-) cdks**

SCHEMATIC REPRESENTATION OF cdk5 and JNK SIGNALING CASCADES IN NEURODEGENERATION



IL-6 induced signal transduction in calcium influx as analyzed with Fluo3 AM

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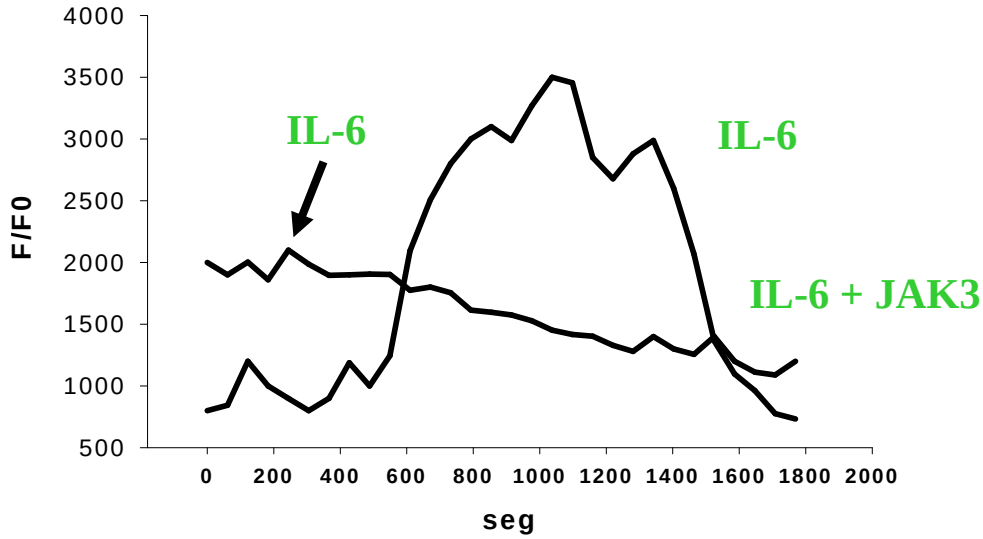

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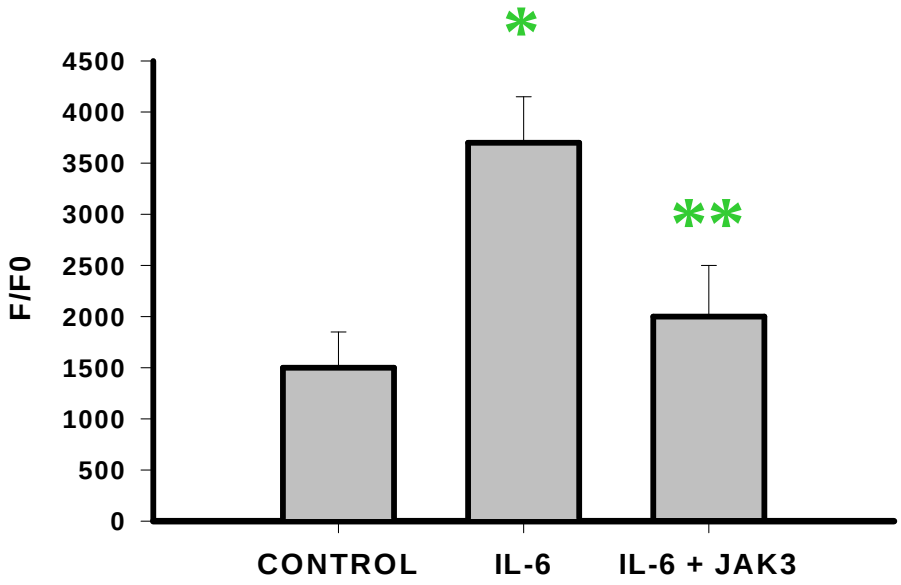
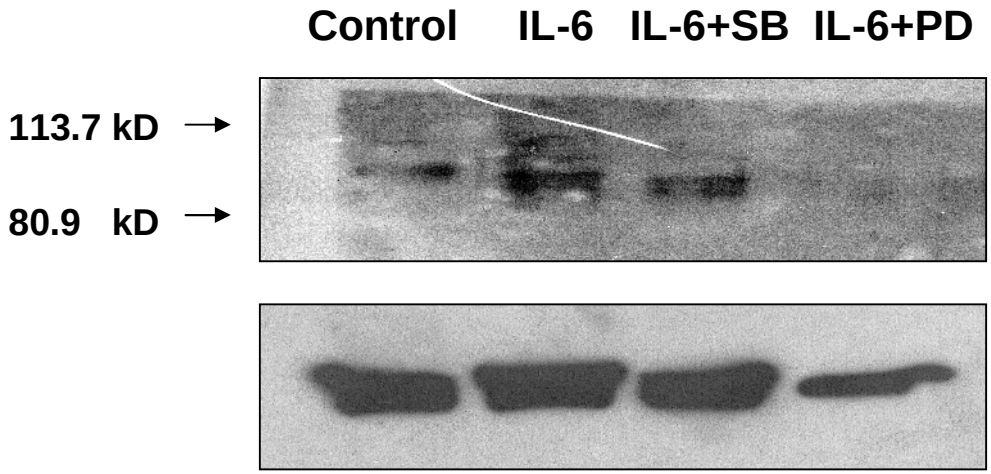


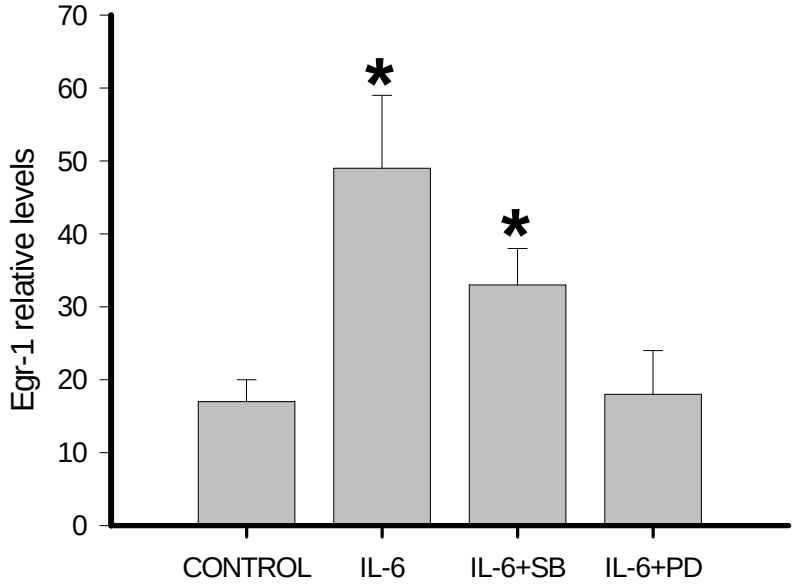
(n=5)

IL-6 INCREASES Egr-1 FACTOR IN HIPPOCAMPAL NEURONS



Egr-1 ANTI Egr1 C 588)

actin



IL-6 (5ng/ml) x 48h

SB: a p38 inhibitor SB3089

PD: MAPK inhibitor PD 98059

MAIN FINDINGS

- **IL-3 IS A NEUROPROTECTOR VIA ACTIVATION OF NEURONAL SURVIVAL FACTORS.**

- **IL-6 and IL-1 INDUCE DEREGULATION OF THE cdk5/p35 COMPLEX AND LEAD TO TAU HYPERPHOSPHORYLATION IN HIPPOCAMPAL CELLS**

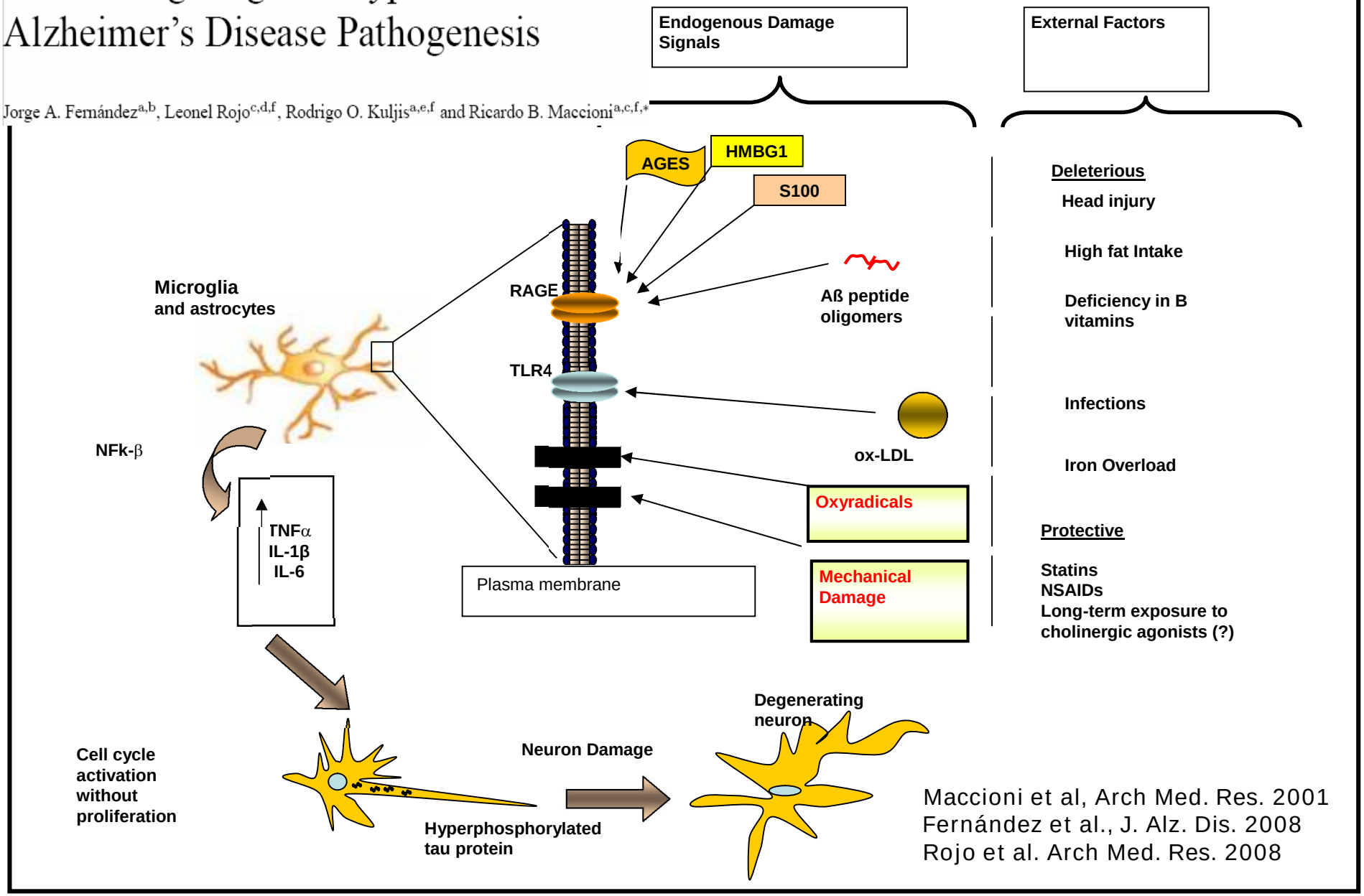
- **JAK/STATs and MAPK-p38 PATHWAYS ARE INVOLVED IN IL-6 AND IL-1 TAU MODIFICATIONS**

- **IL-6 INDUCES AN INCREMENT IN THE CYTOSOLIC CALCIUM THUS AFFECTING TAU PHOSPHORYLATION PATTERNS**

Journal of Alzheimer's Disease 13 (2008) 1–5
IOS Press

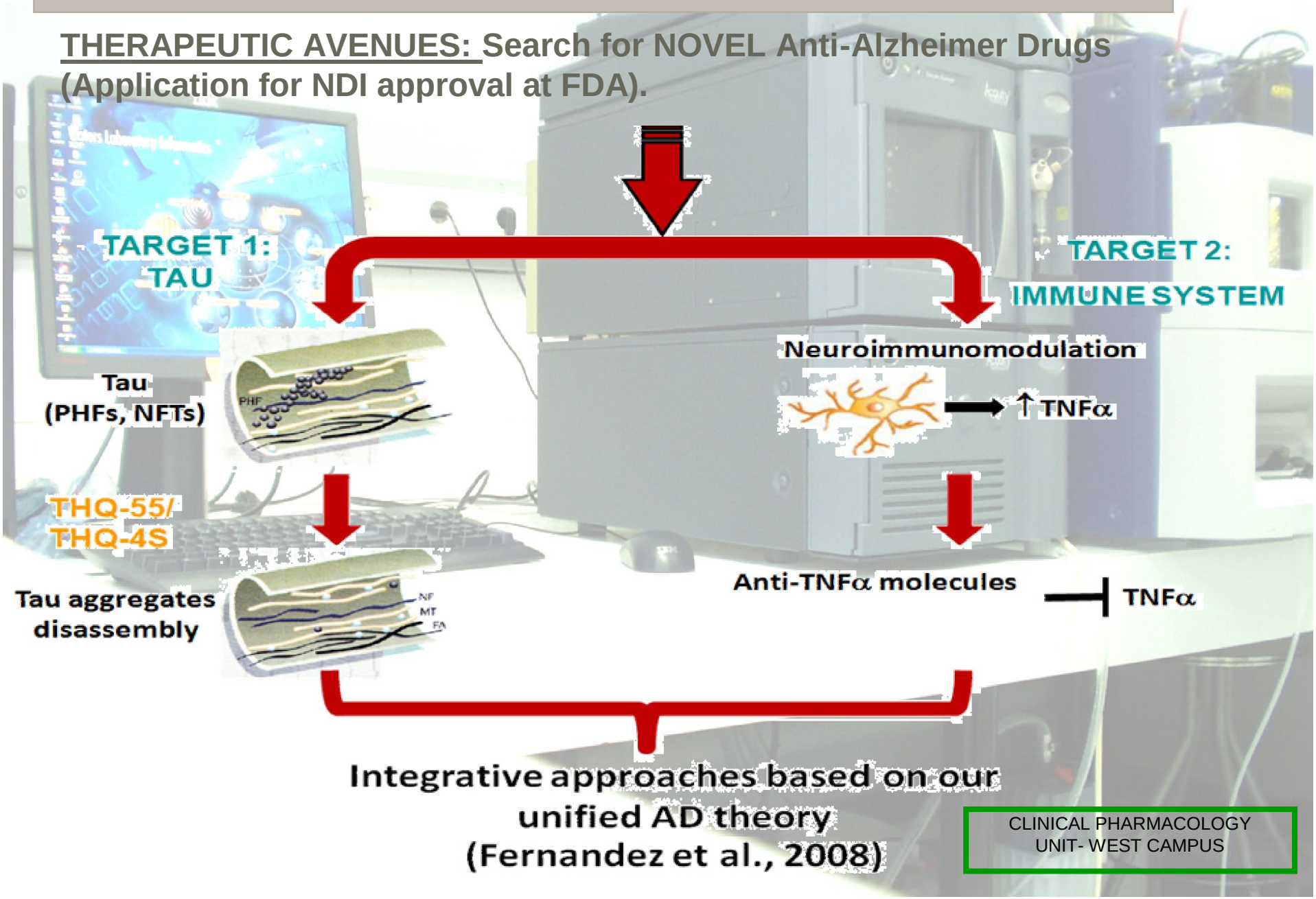
The Damage Signals Hypothesis of Alzheimer's Disease Pathogenesis

Jorge A. Fernández[a,b], Leonel Rojo[c,d,f], Rodrigo O. Kuljis[a,e,f] and Ricardo B. Maccioni[a,c,f,*]



Maccioni et al, Arch Med. Res. 2001
Fernández et al., J. Alz. Dis. 2008
Rojo et al. Arch Med. Res. 2008

THERAPEUTIC AVENUES: Search for NOVEL Anti-Alzheimer Drugs (Application for NDI approval at FDA).



CLINICAL PHARMACOLOGY
UNIT- WEST CAMPUS

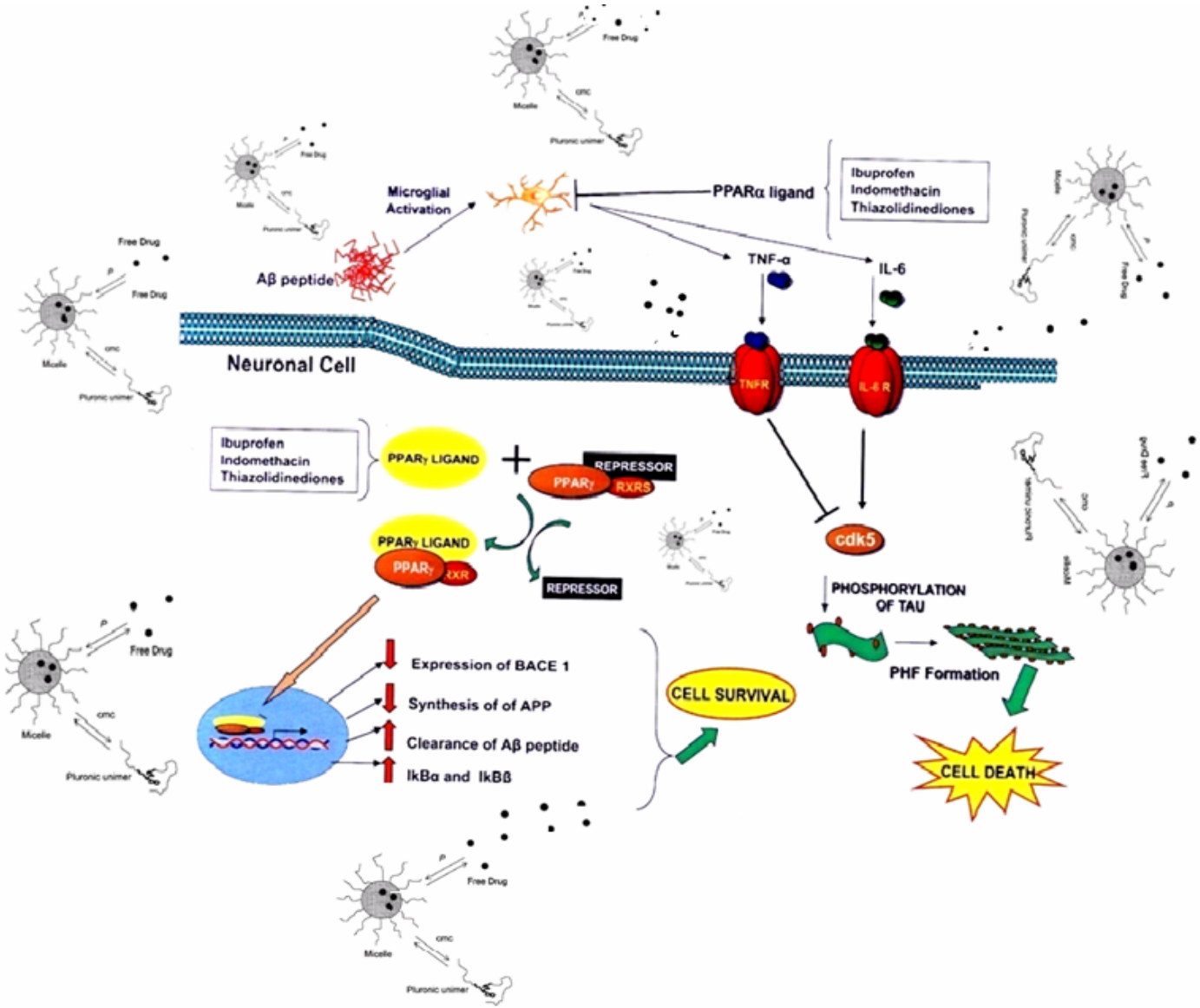
Approaches to anti-inflammatory therapy of AD

1.Block the secreted inflammatory mediators: eg prostaglandins, inflammatory cytokines, complement proteins

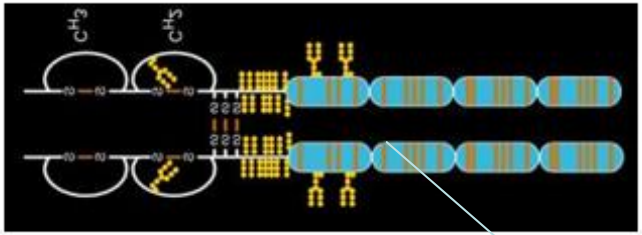
2. Block the intracellular inflammatory pathways: eg Erk1,2; NFkB; JAK-STAT 1,2,3

3. Stimulate the antiinflammatory intracellular pathways: eg convert microglia from the Th-1 type to Th-2 type

These approaches do not overlap so that multiple agents may have synergistic effects

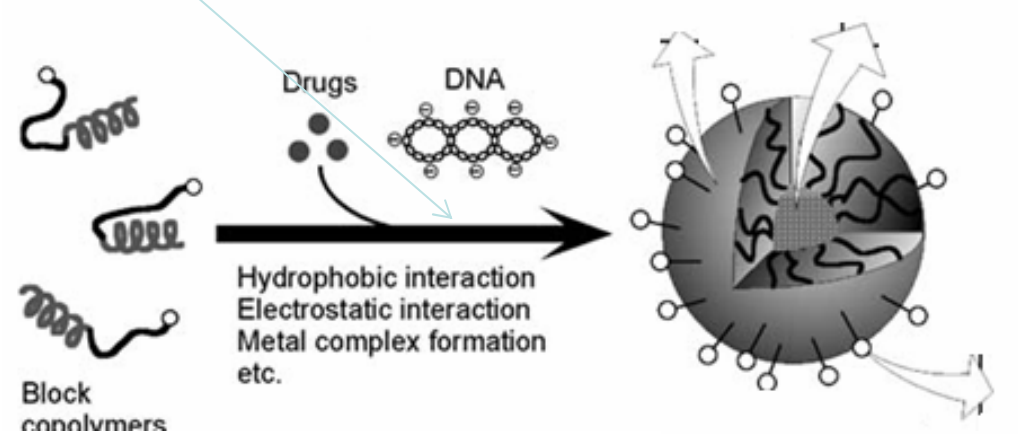


Neuroinflamation: Impplications for the Pathogenesis and Molecular Diagnosis of Alzheimer's Disease. Maccioni and coworkers. Archives of Medical Research 39 (2008) 1-16



STRUCTURE OF ETANERCEPT

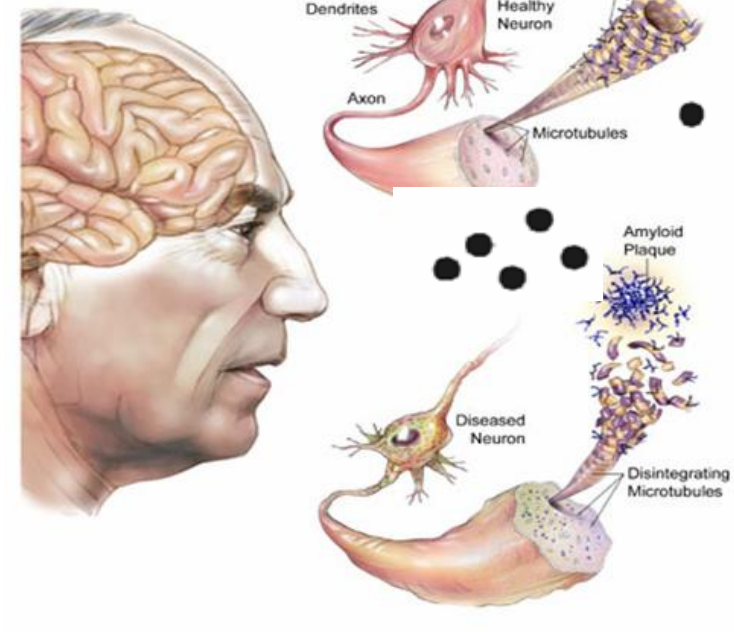
$C_{2224}H_{3475}N_{621}O_{698}S_{36}$; MW: 51,234



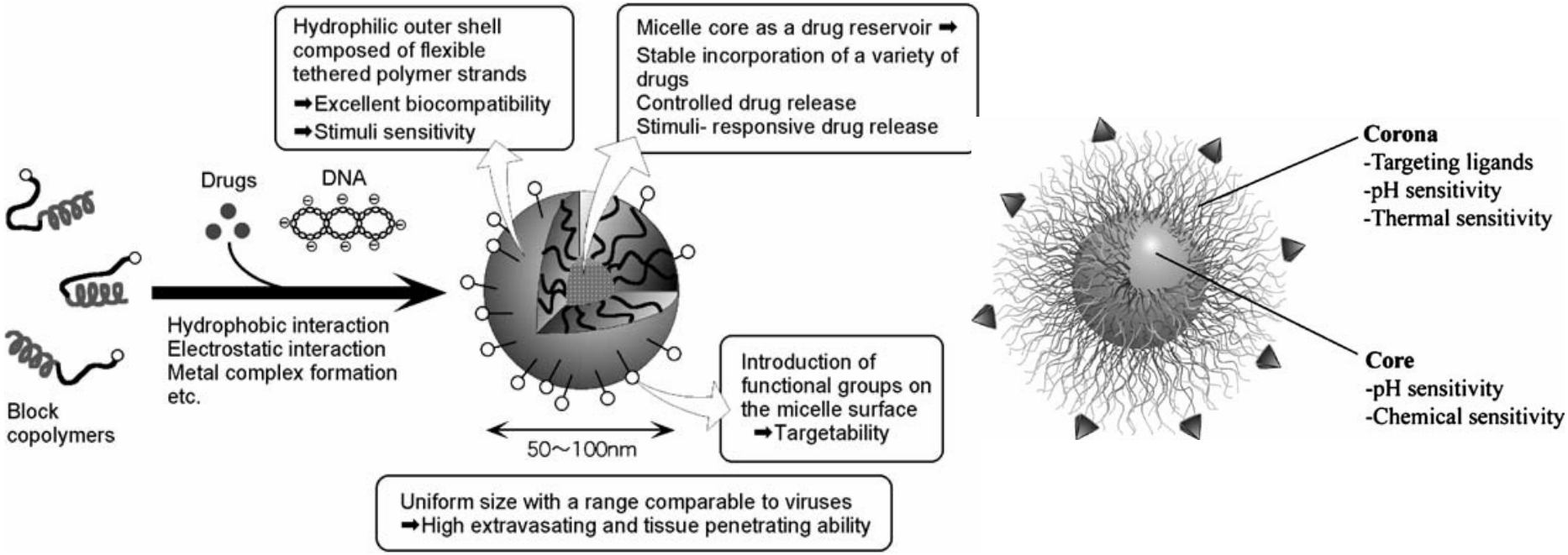
Etanercept is an antiinflammatory drug clinically successful for AD treatment, supporting the neuroimmunomodulation hypothesis.

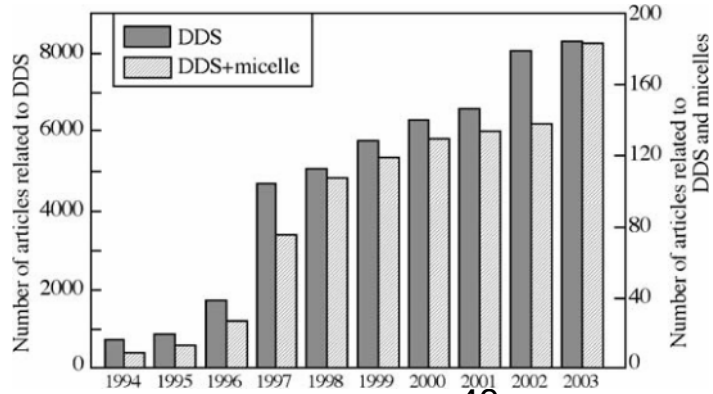
Drug is used via perispinal injection, since it does not pass the blood brain barrier.

USE OF DRUG DELIVERING MICELLES.



POLYMERIC MICELLES FOR DRUG DELIVERY: ETANERCEPT





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Thanks / Gracias

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Endeavors toward quality of life of our citizens.