

**SOCIETAT CATALANA DE FARMACOLOGIA**

# **ESTRATÈGIES DE NEUROPROTECCIÓ EN MALALTIES NEURODEGENERATIVES**

**Dianes terapèutiques en la prevenció de la mort neuronal**

**Dr. Fèlix Junyent**

**La leptina com a molècula neuroprotectora**

**Dr. Jaume Folch**

**22 de Febrer de 2012**

*ciberMed*

**I = B + U B →**



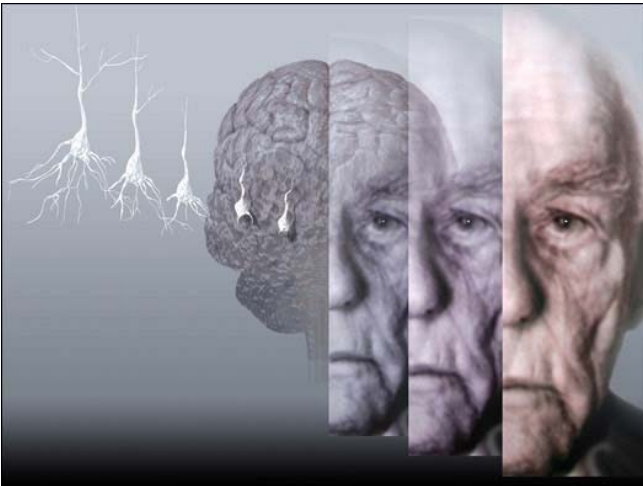
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ROVIRA I VIRGILI

# DIANES TERAPÈUTIQUES EN LA PREVENCIÓ DE LA MORT NEURONAL

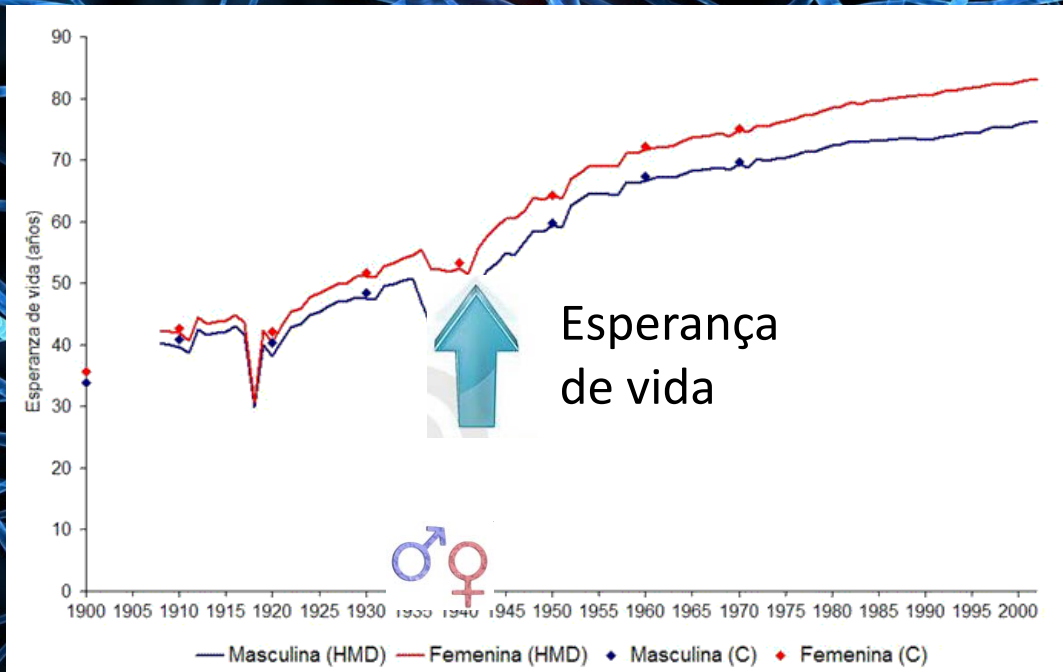
Fèlix Junyent Herena



Percentatge població > de 65 anys



Malalties neurodegeneratives



Fuente: Carreras (1989), Carreras y Tafunell (2003), INE y Human Mortality Database.

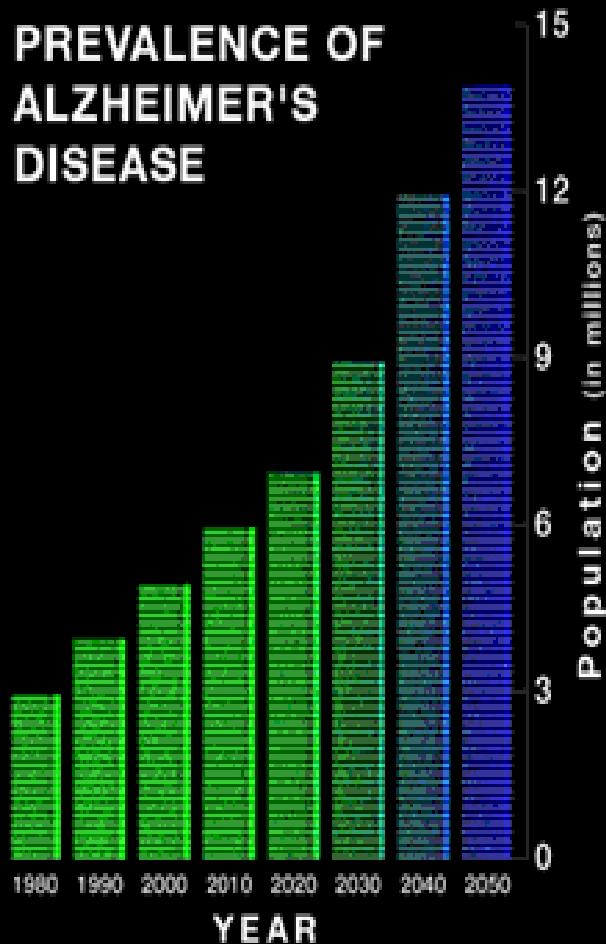
# Causes de la mort neuronal



- ▶ Alteració mitocondrial
- ▶ Estrès oxidatiu
- ▶ Agregació proteica
- ▶ Activació de cinases (GSK3 $\beta$ , CDK5, JNK,...)
- ▶ Excitotoxicitat
- ▶ Inflamació
- ▶ Dany del DNA
- ▶ Activació vies apoptòtiques/autofàgia

# Alzheimer

## PREVALENCE OF ALZHEIMER'S DISEASE



La malaltia de Alzheimer és la forma de demència més comú.

Afecta a més de 8 milions de persones a tot el món i és la tercera causa de mort després de les malalties cardiovasculars i el càncer.

# Alzheimer

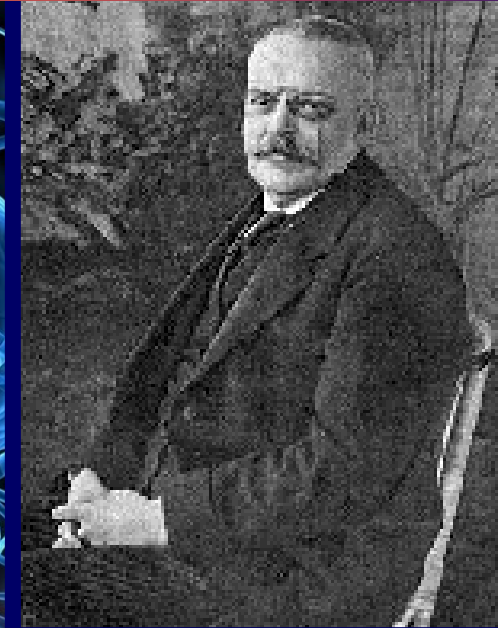


És una malaltia neurodegenerativa progressiva

Afecta al comportament, l'aprenentatge i a l'habilitat de realitzar tasques quotidianes, provocant la pèrdua de independència del pacient.

Actualment és incurable i provoca la mort del pacient.

**ALOIS ALZHEIMER**



**Metge Alemany**

Va seguir el cas de Augusta durant 5 anys en un hospital mental

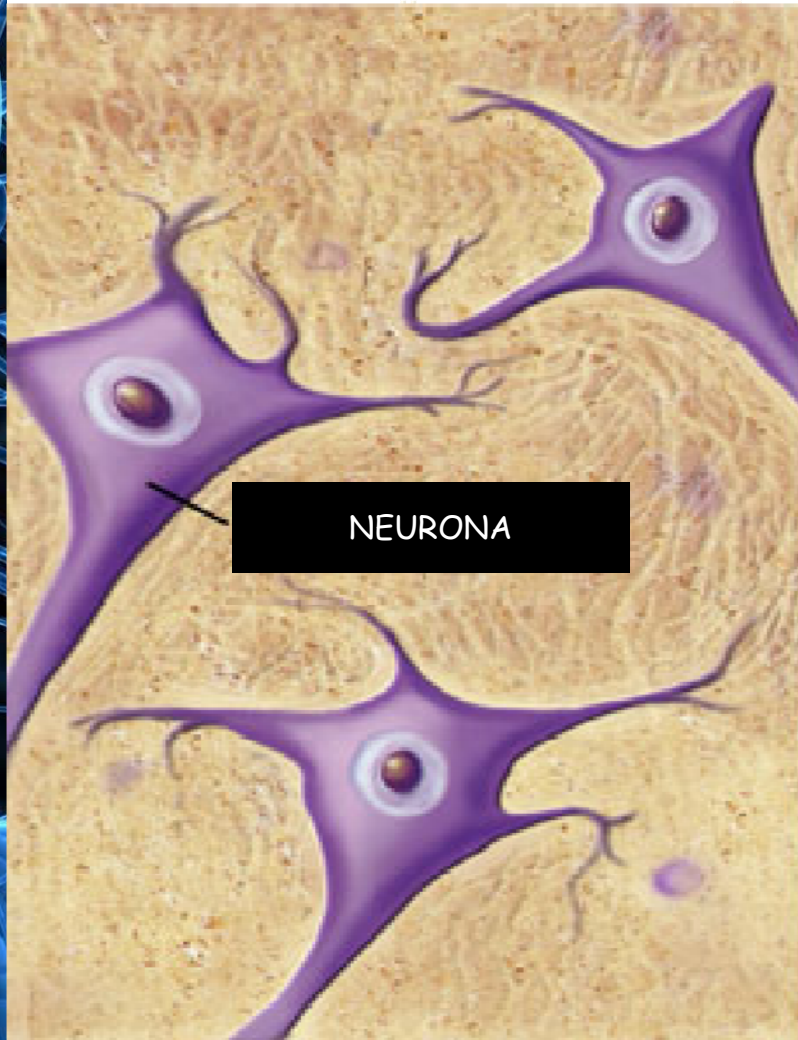
**AUGUSTA D.**



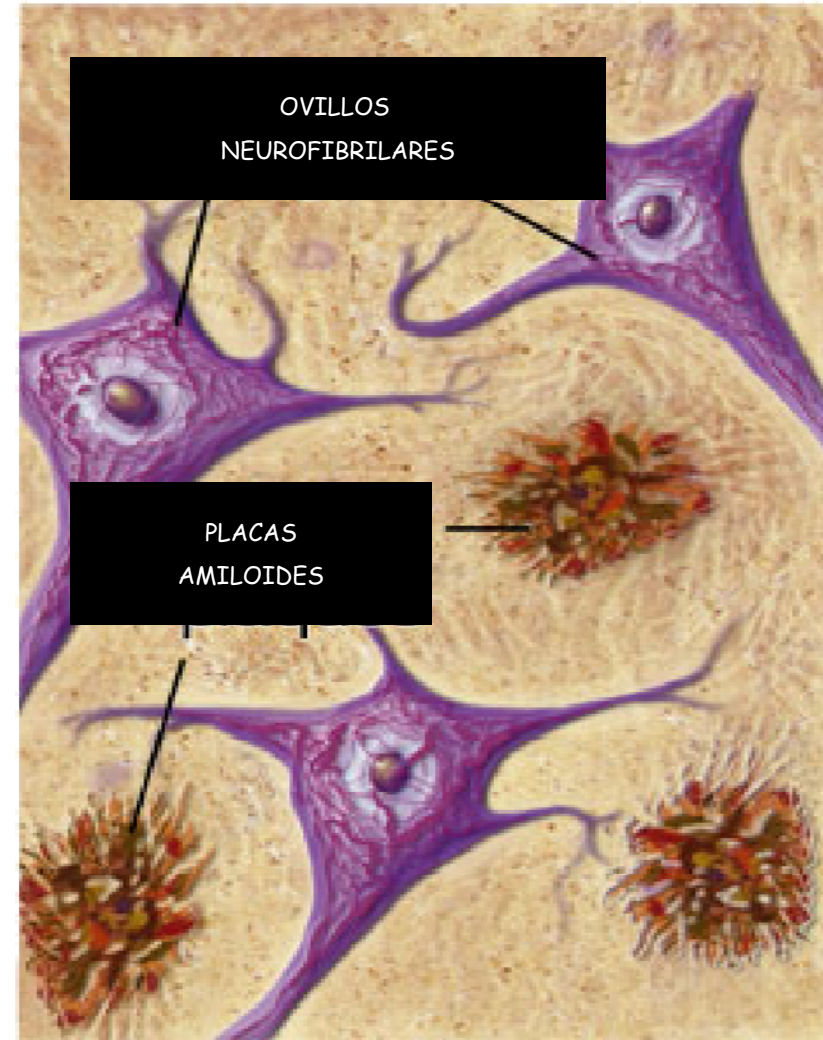
L'autòpsia va revelar alteracions en el cervell (1906)

# Patologia microscòpica

Normal



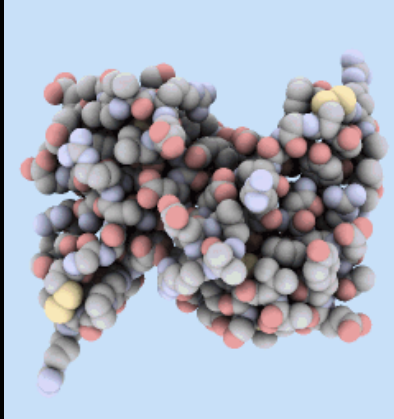
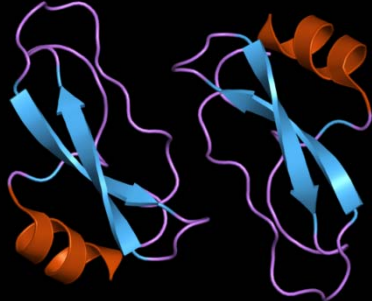
Alzheimer's



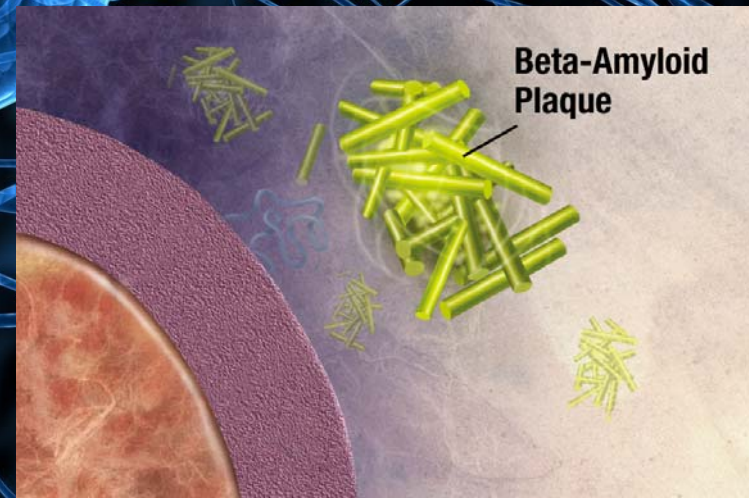
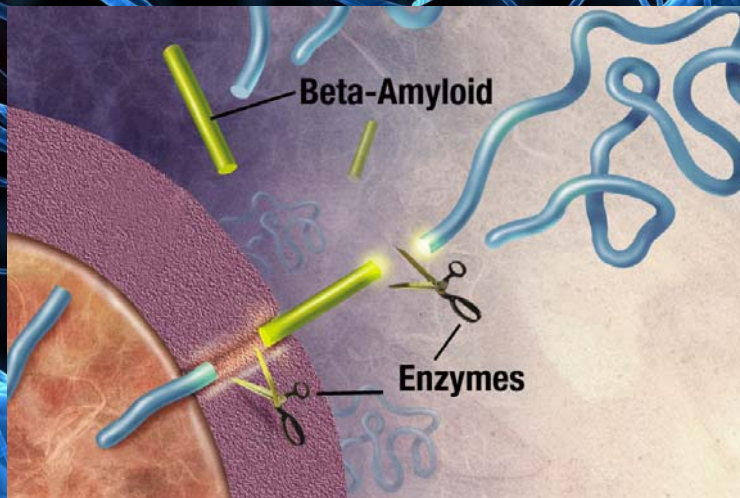
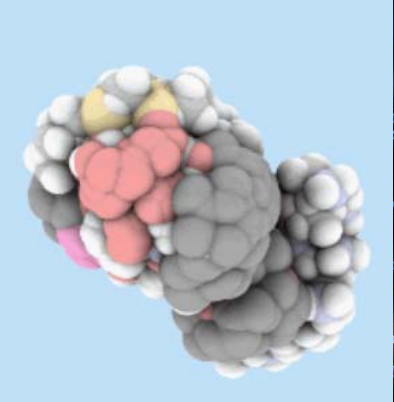
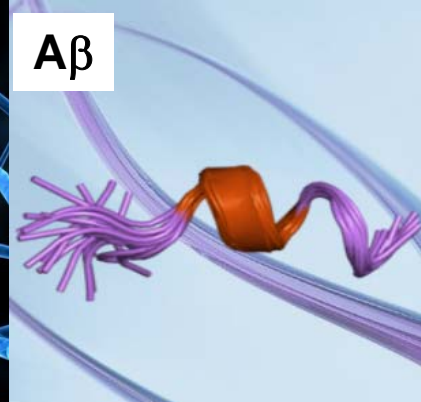


# Formació plaques $\beta$ -amiloide

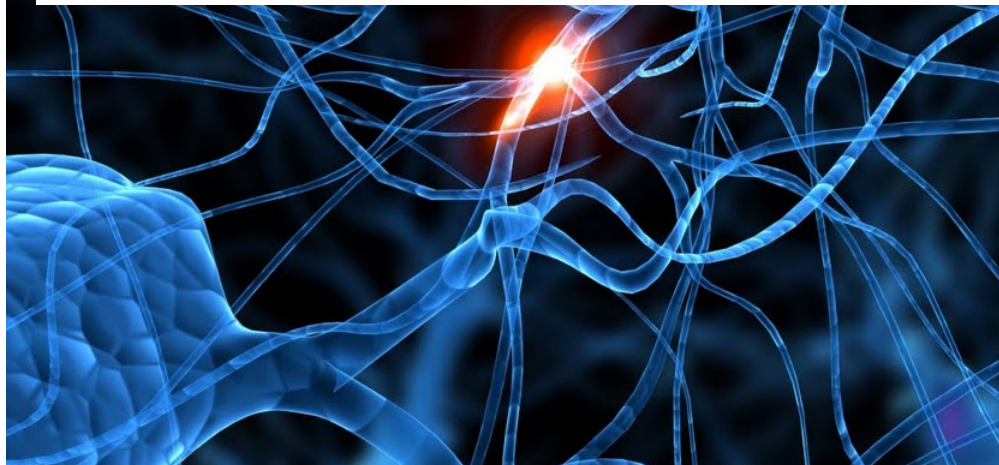
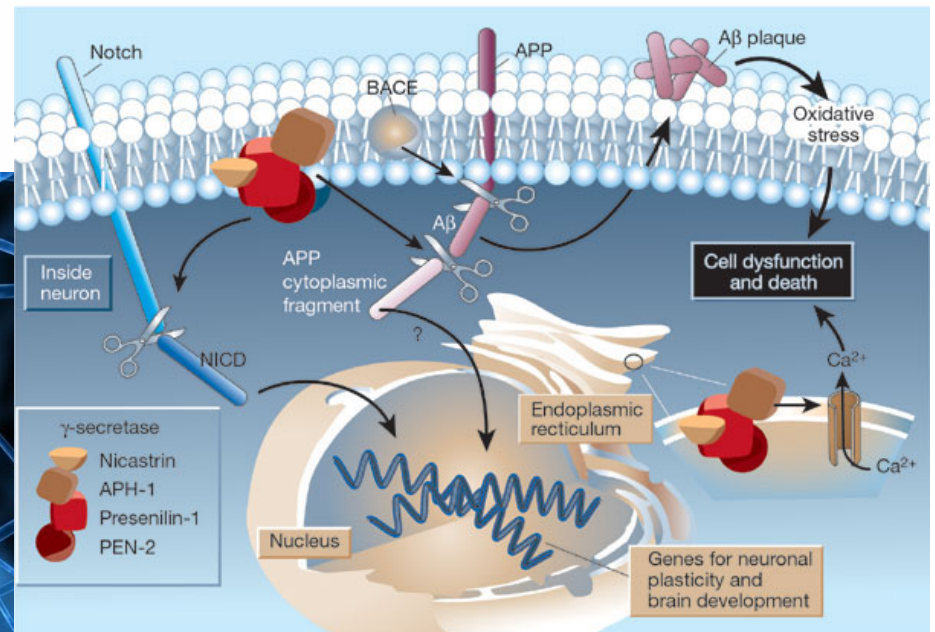
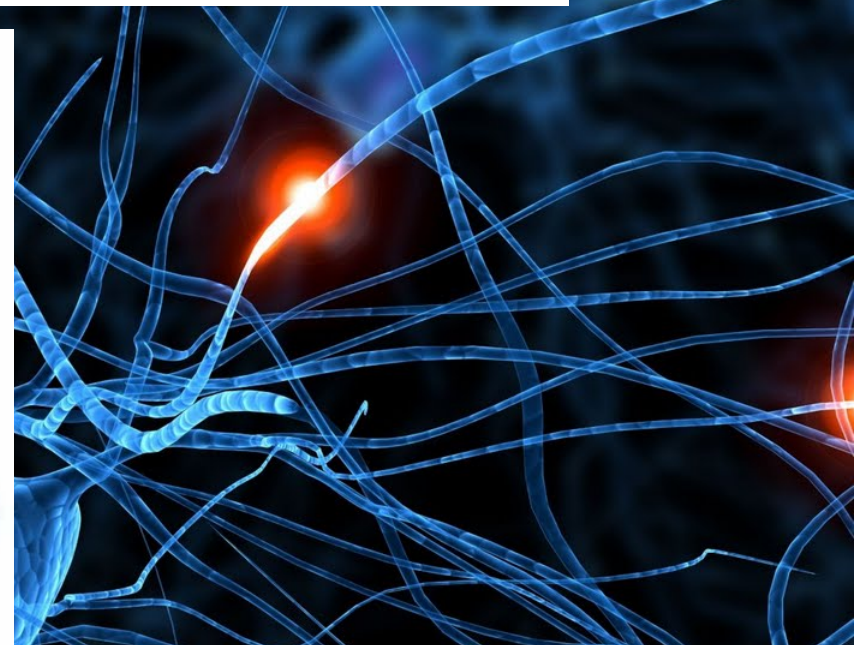
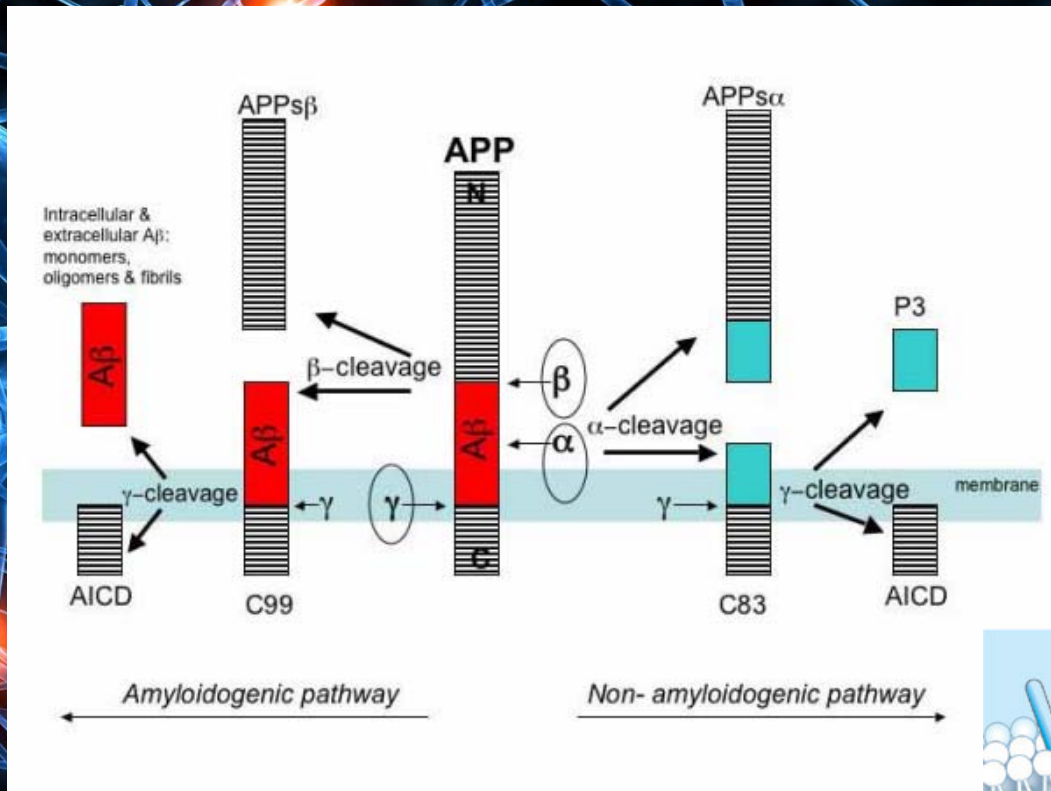
APP



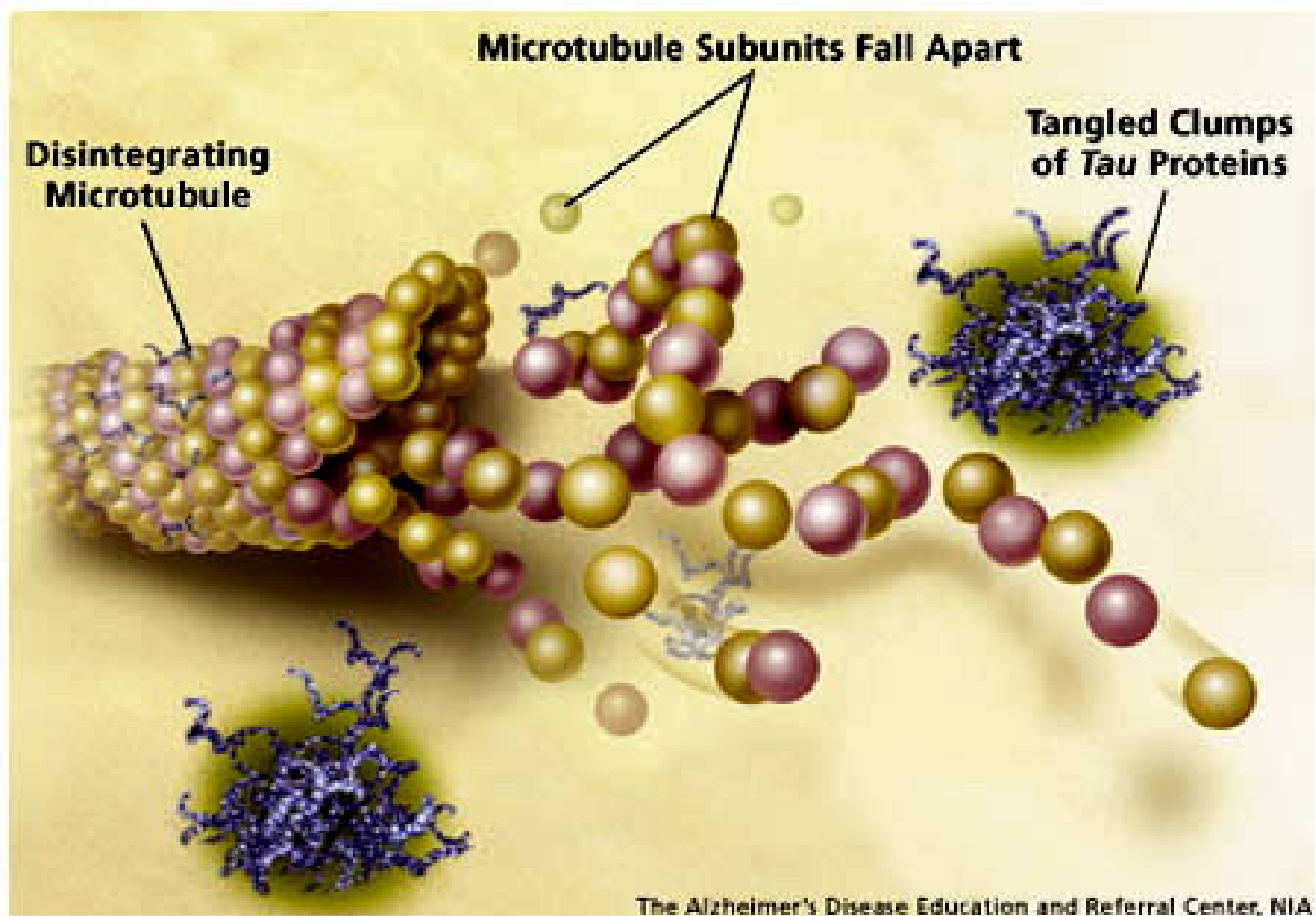
A $\beta$



# Formació plaques $\beta$ -amiloide

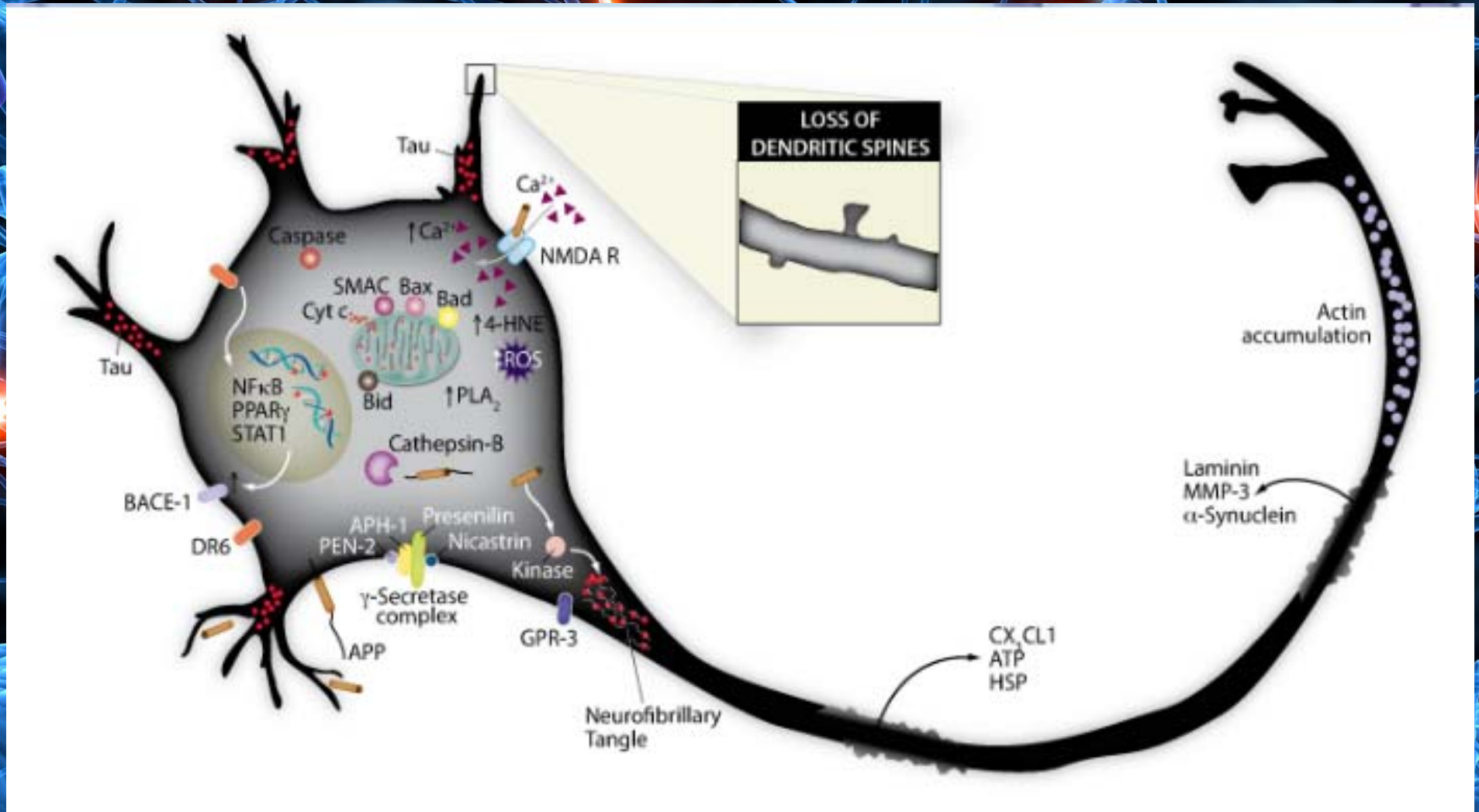


# Fosforilació Tau

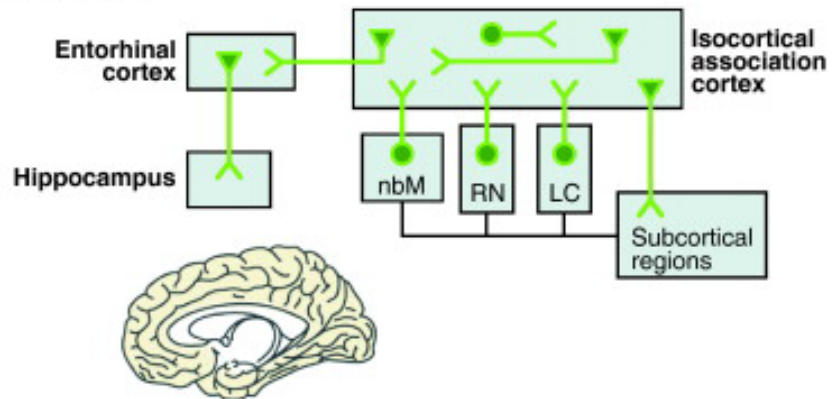


The Alzheimer's Disease Education and Referral Center, NIA

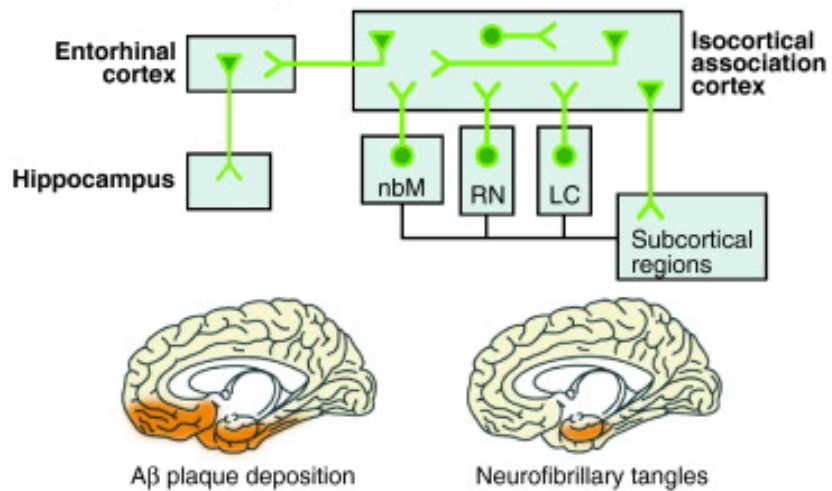
# Pèrdua de la funció sinàptica



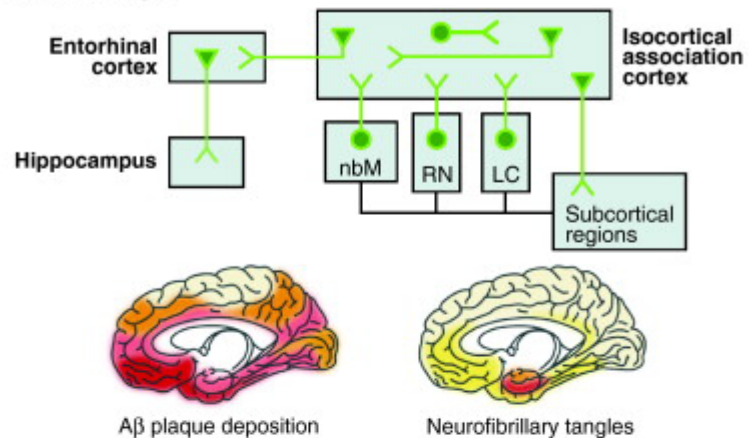
### Normal brain



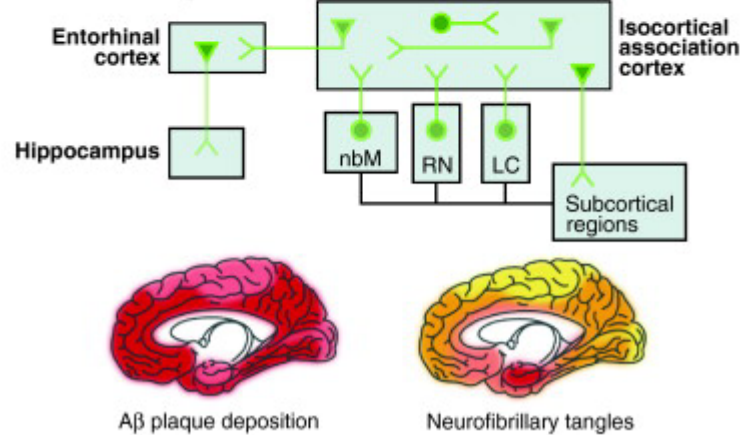
### Transentorhinal stage



### Limbic stage



### Isocortical stage



# Síntomes d'alarma

- 1.- Disminució de la memòria recent que afecta a la realització del treball
- 2.- Dificultats en realitzar treballs familiars
- 3.- Problemes en el llenguatge
- 4.- Desorientació en el temps i l'espai
- 5.- Capacitat disminuïda de jutjar
- 6.- Problemes en el pensament
- 7.- Extraviar les coses
- 8.- Canvis d'ànim i de comportament
- 9.- Canvis en la personalitat
- 10.- Disminució d'iniciativa

# Factors de risc

- Edat avançada
- Historia familiar (factors genètics)
- Síndrome de Down
- Sexe femení

## Causes de la malaltia?

- Dèficit de acetilcolina
- Acumulació de amiloide i/o tau.
- Trastorns metabòlics



# Causes de la mort neuronal en Alzheimer



No s'ha determinat exactament el procés etiopatogènic

Interacció entre susceptibilitat genètica, envelliment, factors mediambientals i estil de vida

# Causes de la mort neuronal en Alzheimer



$\beta$ -Amiloide

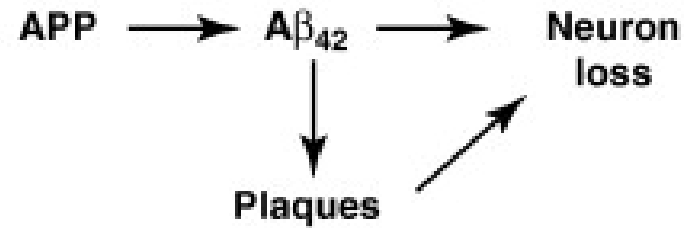
Tau fosforilada

Estrès oxidatiu (mitocondri)

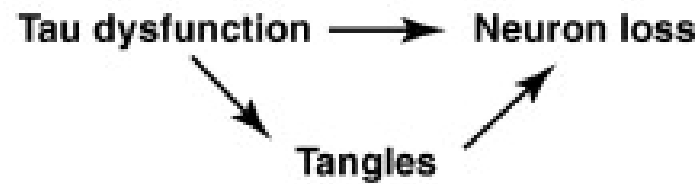
Excitotoxicitat

Inflamació

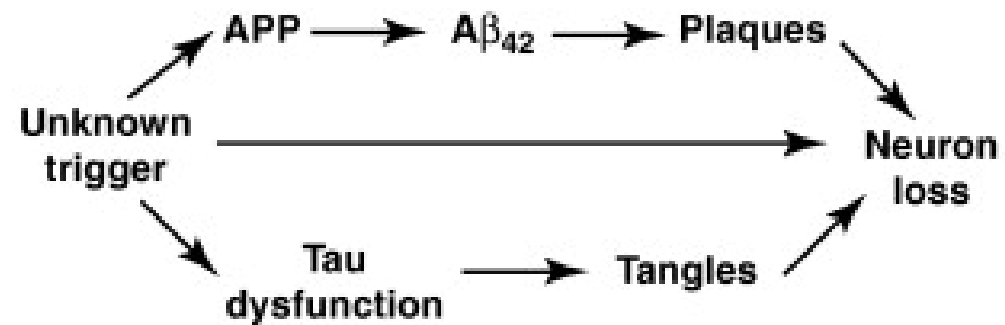
**(a) Amyloid hypothesis**



**(b) Tau hypothesis**



**(c) Unknown trigger hypothesis**



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Review (16294)

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Molecular Basis of Inhibitory Activities of Berberine against Pathogenic Enzymes in Alzheimer's Disease.

1. Ji HF, Shen L.

ScientificWorldJournal. 2012;2012:823201. Epub 2012 Jan 4.

PMID: 22262957 [PubMed - in process]

The DNA replication stress hypothesis of Alzheimer's disease.

2. Yurov YB, Vorsanova SG, Iourov IY.

ScientificWorldJournal. 2011;11:2602-12. Epub 2012 Jan 2.

PMID: 22262948 [PubMed - in process]

Cdk5/p25-Induced Cytosolic PLA2-Mediated Lysophosphatidylcholine Production Regulates Neuroinflammation and Triggers

3. Neurodegeneration.

Related searches

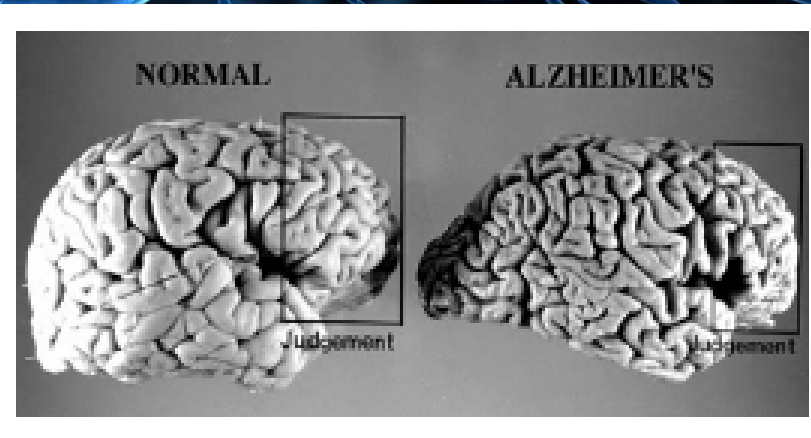
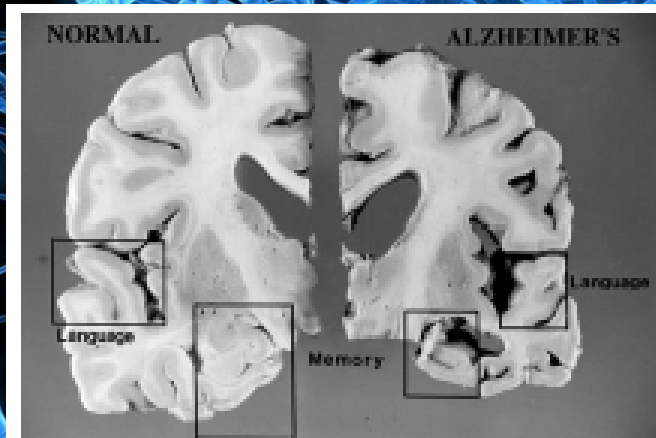
alzheimer's disease review

alzheimer's disease treatment

alzheimer's disease amyloid

alzheimer's disease tau

biomarkers alzheimer's disease



## Global deterioration scale (GDS) de Reisberg

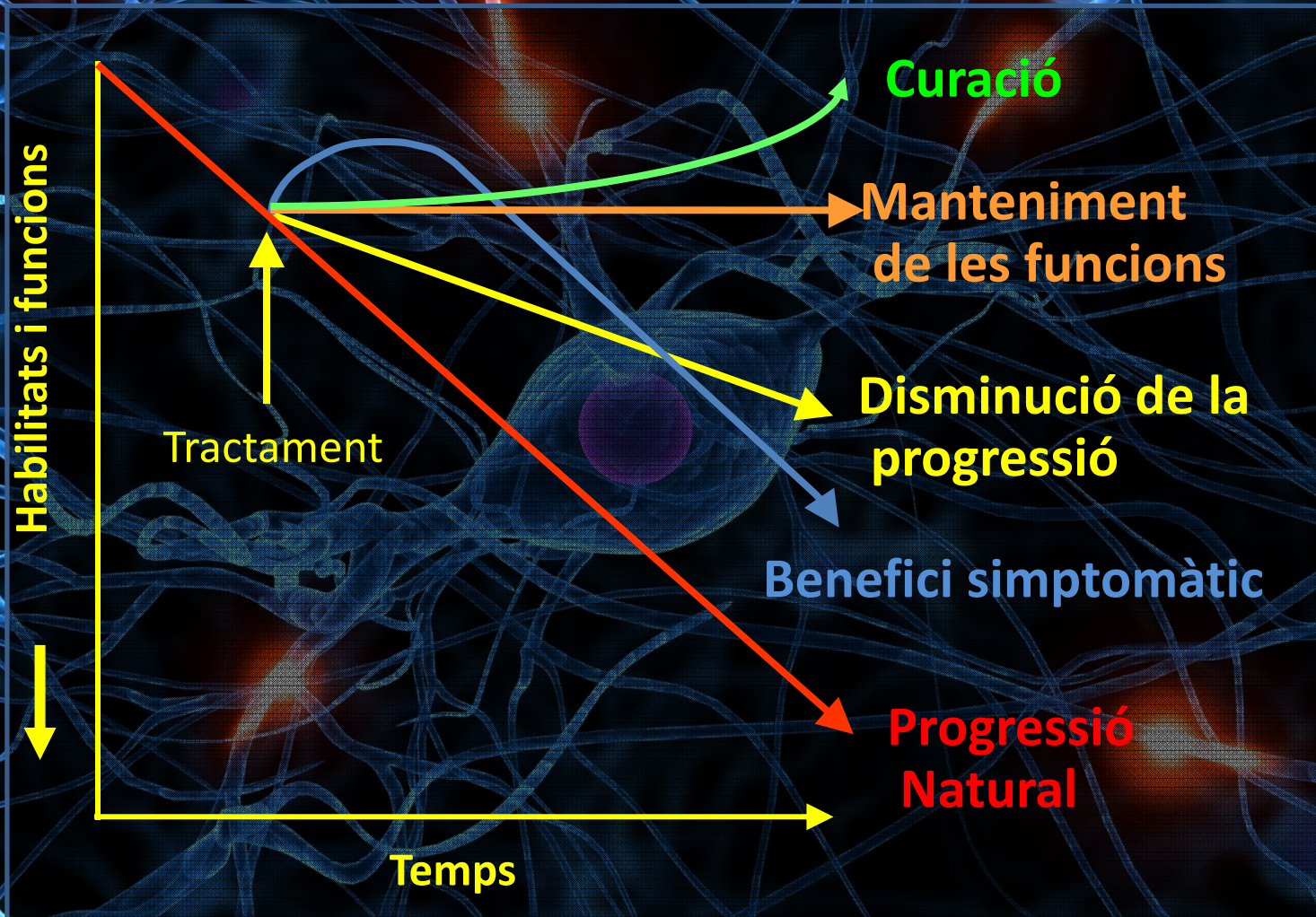
1. Absència de dèficit cognitiu
2. Dèficit cognitiu molt lleu
3. Dèficit cognitiu lleu
4. Dèficit cognitiu moderat
5. Dèficit cognitiu moderadament greu
6. Dèficit cognitiu greu
7. Dèficit cognitiu molt greu

**Fase preclínica**

**→ Detecció de la malaltia**

**Fase clínica**

# TRACTAMENTS



# OBJECTIUS DEL TRACTAMENT



REDUIR LA PRODUCCIÓ I ACUMULACIÓ DE  $A\beta$

DISMINUIR ELS DIPÒSITS DE  $A\beta$  FORMATS

MILLORAR LA FUNCIÓ SINÀPTICA

PROTEGIR LES NEURONES DE LA MORT

INHIBIR EL PROCÉS INFLAMATORI

INHIBIR L'ESTRÈS OXIDATIU

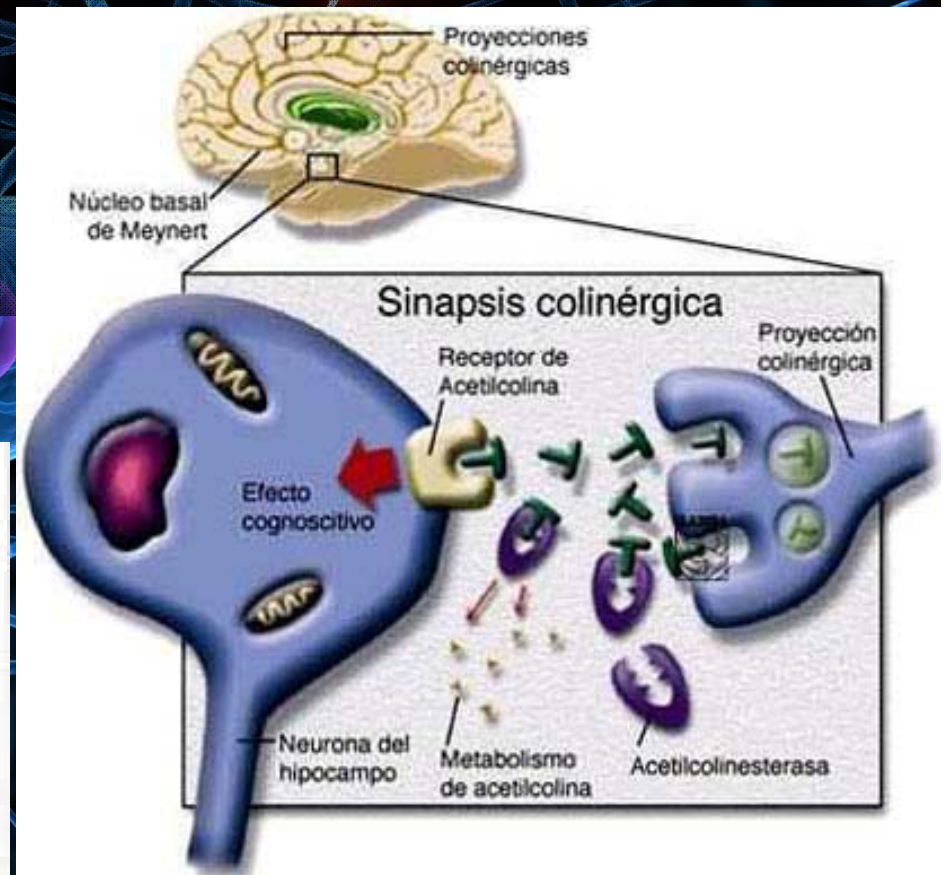
# Millora de la simptomatologia:

## Inhibidors de la acetilcolinestasa

- Tacrina (Cognex®)
- Donezepilo (Aricept®)
- Rivastigmina (Exelon®)
- Galantamina (Reminyl®)



- 1) Aumentada disponibilitat de ACh a nivell sinàptic (AChE inhibició)
- 2) Aumentada alliberació de ACh en l'espai intersinàptic (modulació al·lostèrica dels receptors nicotínics presinàptics)







Millora de la simptomatologia:

Modulació neurotransmissió glutamatèrgica

- Memantina (Ebixa®): antagonista no competitiu del receptor NMDA

Bloqueig de receptors 5-HT6

S'afavoreix la neurotransmissió colinèrgica  
Millora de les capacitats cognitives

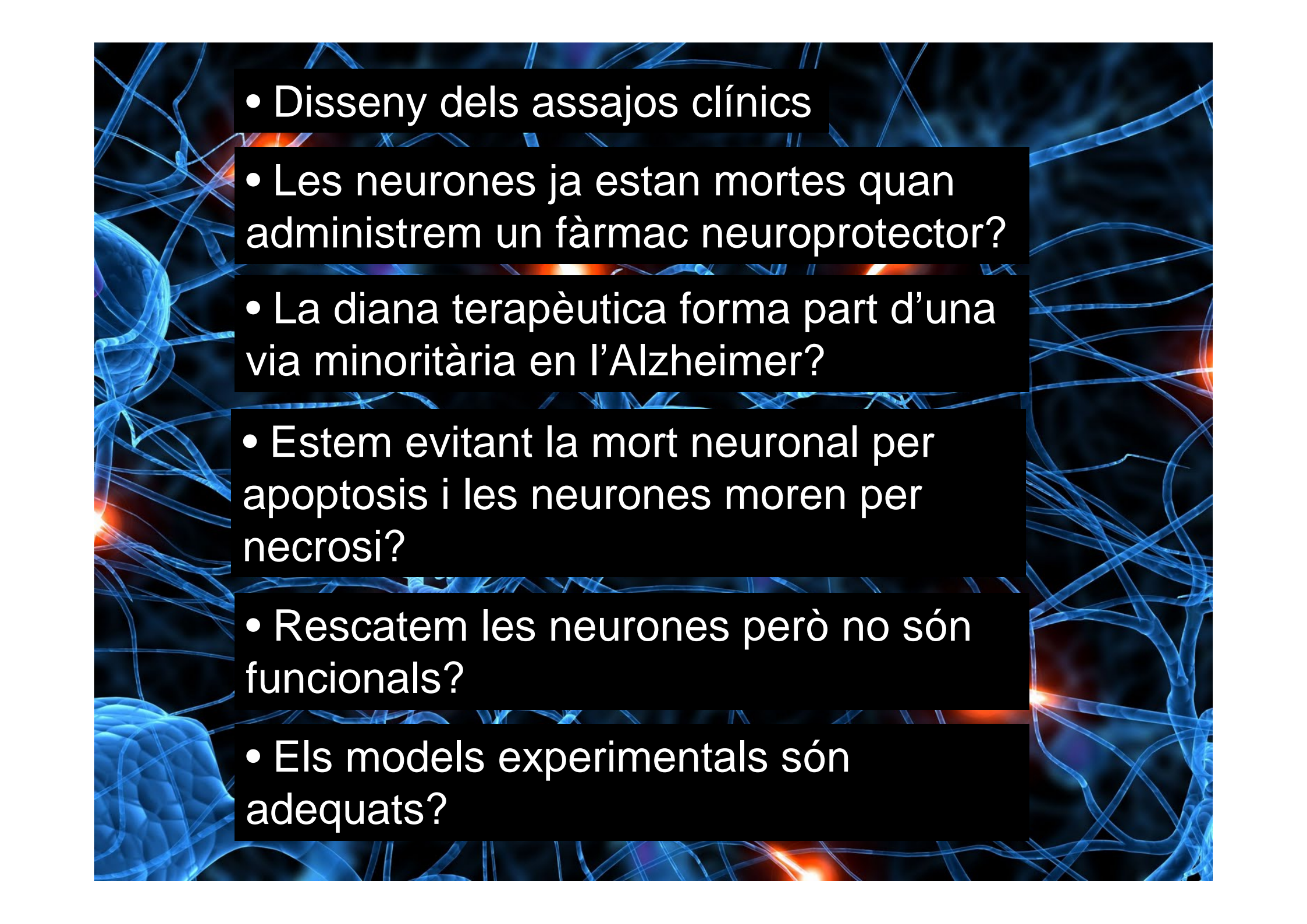
## Trends in pharmacological Sciences 32: 141-147; 2011

**Table 1. Completed and current phase III clinical trials of potential neuroprotective therapeutics for Alzheimer's disease**

Compound	Type of molecule	Mechanism of action	Number of patients	Status	Refs
Arovastin	Small molecule	HMG CoA-reductase inhibitor	600	No efficacy	[55]
Ginko biloba	Herbal extract	Unknown	3069	No efficacy	[45]
NSAIDS <sup>a</sup>	Small molecules	Anti-inflammatory	>2500	No efficacy	[56-61]
Simvastatin	Small molecule	HMG CoA-reductase inhibitor	400	No efficacy	[62]
Tarenflurbil	Small molecule	Reduces A $\beta$ concentration ( $\gamma$ -secretase modulator)	1600	No efficacy	[63]
Rosiglitazone	Small molecule	PPAR $\gamma$ agonist	3713	No efficacy	[64]
Tramiprosate (homotaurine)	Small molecule	Reduces A $\beta$ concentration	1052	No efficacy	[64]
Xaliproden	Small molecule	5HT <sub>1A</sub> receptor agonist	2761	No efficacy	[64]
Valproate	Small molecule	GABA <sub>A</sub> receptor agonist and sodium channel blocker	300	No efficacy	[65]
Alpha-tocopherol	Small molecule	Antioxidant	840 and 10 400 with memantine and selenium, respectively	No efficacy	[66]
Docosahexanoic acid (DHA)	Long chain fatty acid	Membrane precursor	400	No efficacy	[39]
LY2062430 Solanezumab	Humanised monoclonal antibody against A $\beta$	Removal of A $\beta$ peptide	Not declared	Ongoing	
LY450139 Semagacestat	Small molecule	$\gamma$ -Secretase inhibitor	2600	No efficacy	[32]
Dimebon	Small molecule	H1-histamine receptor with neuroprotective activity	2825	No efficacy	[38]
Bapineuzumab	Humanised monoclonal antibody against A $\beta$	Removal of A $\beta$ peptide	3850	Ongoing	[29]
ELND005 (AZD-103)	Scyllo-inositol	Preventing and reversing the fibrillisation of A $\beta$	?	About to commence	

A 3D rendering of a complex neural network. The image features a dense web of glowing blue fibers, representing axons and dendrites, set against a dark blue background. Several bright orange and red light flares are scattered throughout the network, suggesting points of high activity or signal transmission. In the center of the network, a prominent, glowing purple sphere is visible, which could represent a specific neuron or a cluster of cells. The overall aesthetic is futuristic and scientific, emphasizing the intricate and dynamic nature of the brain's neural pathways.

Per què els fàrmacs no funcionen?

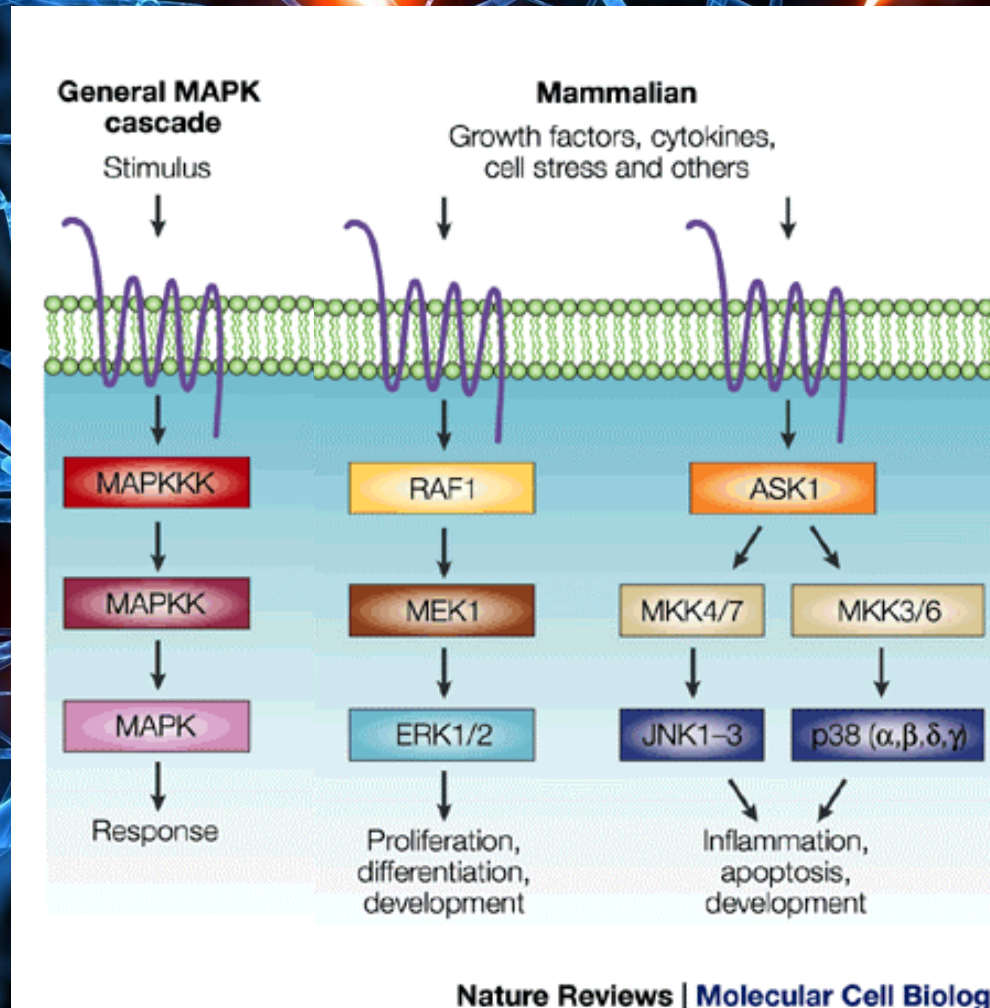
- 
- Disseny dels assajos clínics
  - Les neurones ja estan mortes quan administrem un fàrmac neuroprotector?
  - La diana terapèutica forma part d'una via minoritària en l'Alzheimer?
  - Estem evitant la mort neuronal per apoptosis i les neurones moren per necrosi?
  - Rescatem les neurones però no són funcionals?
  - Els models experimentals són adequats?

# JNK COM A DIANA TERAPÈUTICA PER A LA NEUROPROTECCIÓ



# VIA DE SENYALITZACIÓ DE LES MAPK

Mitogen-activated protein kinase (MAPK)



# VIA DE LA JNK

Jun N-terminal kinase/Stress activated protein kinase

MAPKKK

MAPKK

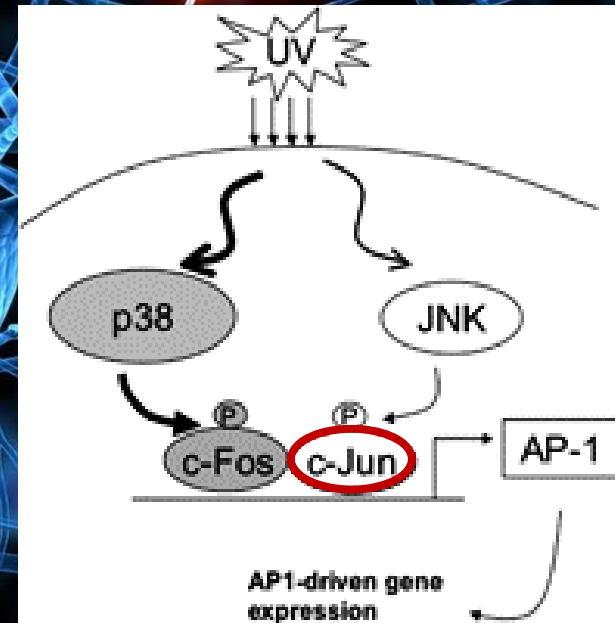
MAPK

MEKK 1, 4  
MLKS; ASK1

MKK 4/7

JNK 1, 2, 3

ATF2, c-JUN,  
Elk1, p53,  
NFAT1/4



# VIA DE LA JNK I NEUROPROTECCIÓ

JNK1/2

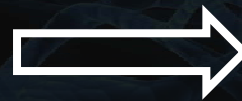


Expressades en  
tot l'organisme

JNK3



Localitzada  
principalment en el  
sistema nerviós



JNK3: La isoforma més  
relacionada amb  
processos apoptòtics  
neuronal



# JNK3 I NEUROPROTECCIÓ

**letters to nature**

## **Absence of excitotoxicity-induced apoptosis in the hippocampus of mice lacking the Jnk3 gene**

Derek D. Yang<sup>\*†‡</sup>, Chia-Yi Kuan<sup>‡§</sup>, Alan J. Whitmarsh<sup>†||</sup>, Mercedes Rincón<sup>\*¶</sup>, Timothy S. Zheng<sup>\*</sup>, Roger J. Davis<sup>†||</sup>, Pasko Rakic<sup>§</sup> & Richard A. Flavell<sup>\*†</sup>

*\* Section of Immunobiology, † Howard Hughes Medical Institute, and § Section of Neurobiology, Yale University School of Medicine, New Haven, Connecticut 06510, USA*

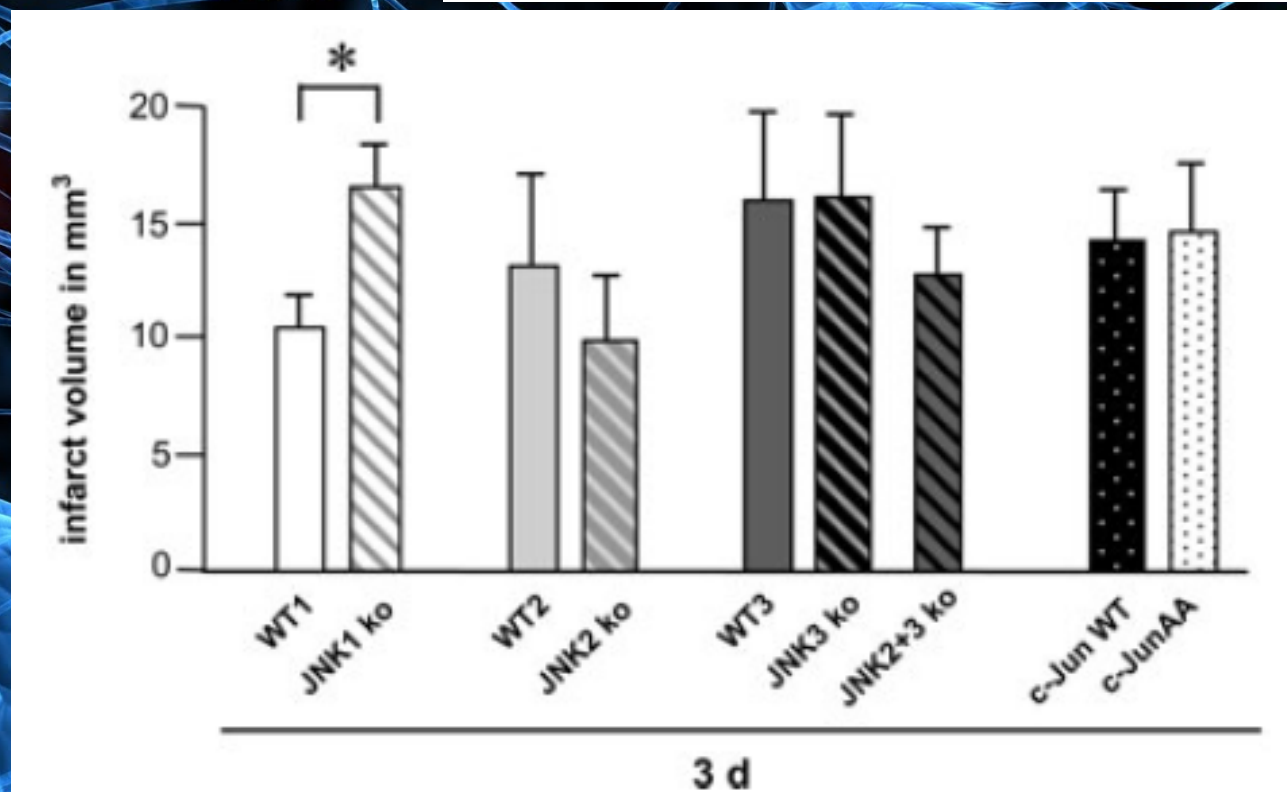
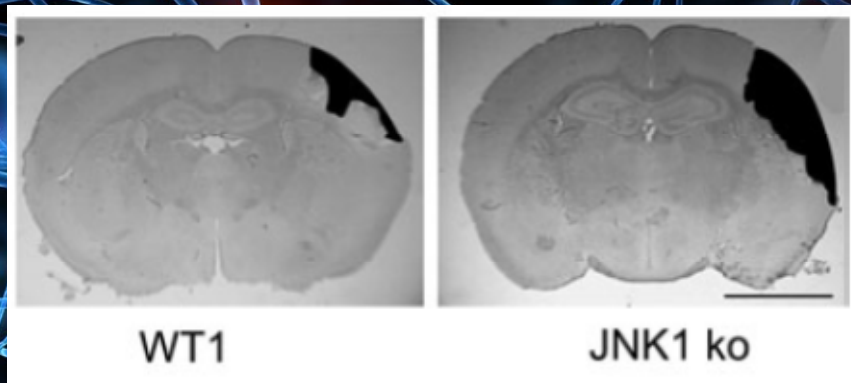
*† Howard Hughes Medical Institute and || Program in Molecular Medicine, Department of Biochemistry and Molecular Biology, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA*

*¶ Immunobiology Program, Department of Medicine, University of Vermont, Burlington, Vermont 05405, USA*

*‡ These authors contributed equally to this work*

**JNK3 possible diana per a la protecció de la mort neuronal**

# IMPLICACIÓ DE JNK EN ISQUÈMIA



**Negative Result**

*Journal of Cerebral Blood Flow & Metabolism*, (5 October 2011) | doi: 10.1038/jcbfm.2011.140

**Lack of neuroprotection of inhibitory peptides targeting Jun/JNK after transient focal cerebral ischemia in Spontaneously Hypertensive rats**

William R Gow, Kym Campbell, Amanda J Meade, Paul M Watt, Nadia Milech, Neville W Knuckey and Bruno P Meloni

11980 • The Journal of Neuroscience, August 17, 2011 • 31(33):11980–11991

Neurobiology of Disease

**Palmitoyl Acyltransferase zD17 Mediates Neuronal Responses in Acute Ischemic Brain Injury by Regulating JNK Activation in a Signaling Module**

Guang Yang and Max S. Cynader  
Brain Research Centre, Vancouver, British Columbia, Canada, V6T 2B5

ORIGINAL ARTICLE

**Excitotoxicity-induced endocytosis mediates neuroprotection by TAT-peptide-linked JNK inhibitor**

Anne Vaslin, Sonia Naegele-Tollardo, Julien Puyal, Peter G. H. Clarke

Article first published online: 9 NOV 2011

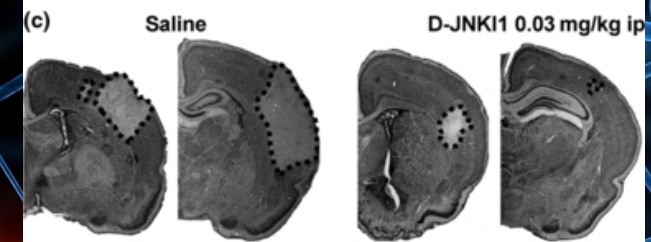
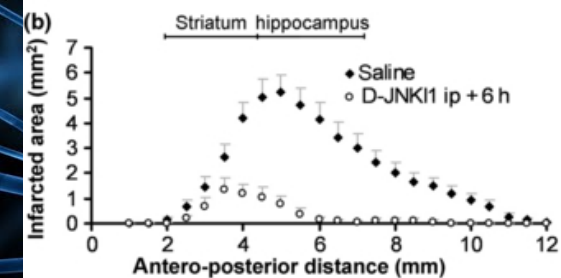
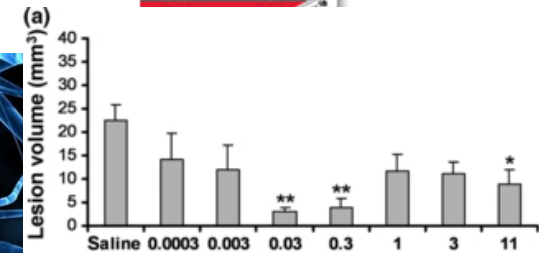
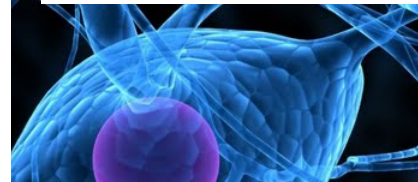
DOI: 10.1111/j.1471-4159.2011.07535.x

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Issue

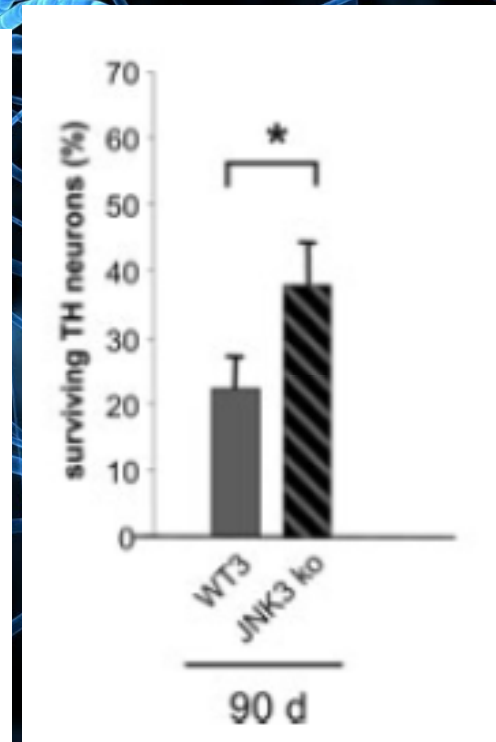
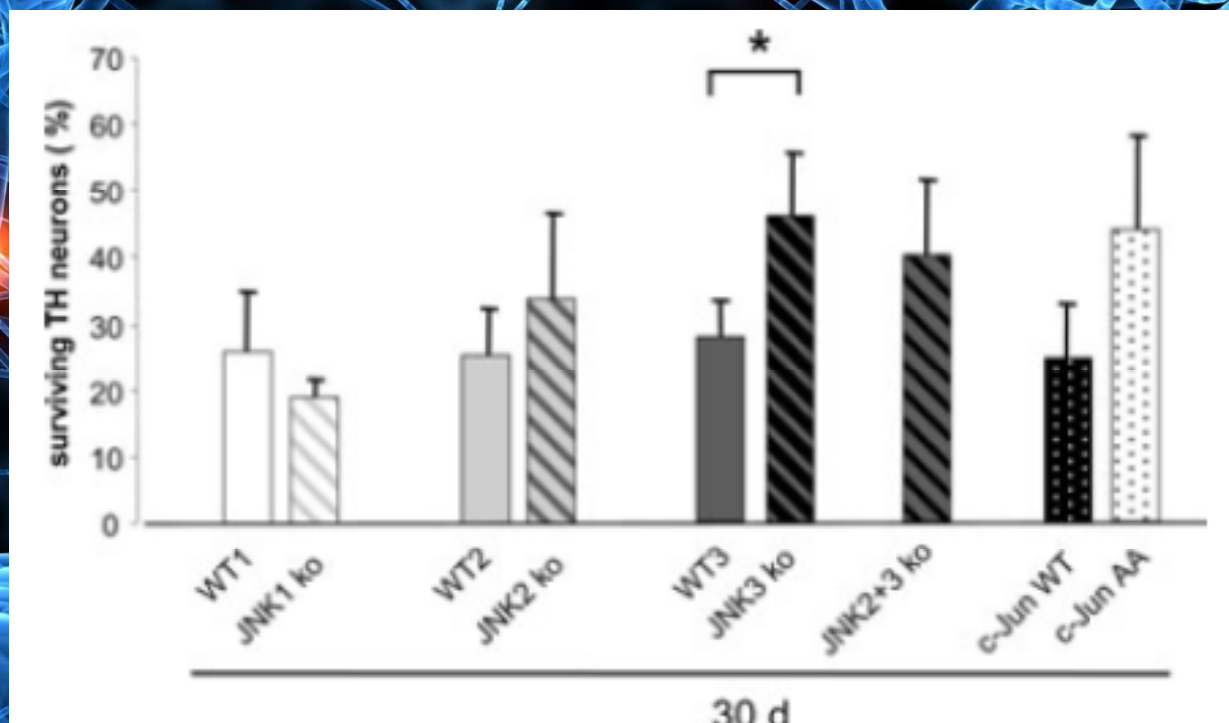


Journal of Neurochemistry  
Early View (Online Version of Record published before inclusion in an issue)



# IMPLICACIÓ DE JNK EN PARKINSON

Supervivència de neurones Tirosina Hidroxilasa (TH) positives en la substància nigra compacta (SNC) després de axotomització



ORIGINAL ARTICLE

# JNK3 Mediates Paraquat- and Rotenone-Induced Dopaminergic Neuron Death

Won-Seok Choi, PhD, Glen Abel, BS, Heather Klintworth, MS,  
Richard A. Flavell, PhD, and Zhengui Xia, PhD

Laboratory Investigation (2010) 90, 156–167

Small peptide inhibitor of JNKs protects against MPTP-induced nigral dopaminergic injury via inhibiting the JNK-signaling pathway

Jing Pan<sup>1,2</sup>, Jing Qian<sup>1</sup>, Yu Zhang<sup>1,2</sup>, Jianfang Ma<sup>2</sup>, Gang Wang<sup>2</sup>, Qin Xiao<sup>2</sup>, Shengdi Chen<sup>1,2</sup> and Jianqing Ding<sup>1,2</sup>

Neurochemistry International 54 (2009) 418–425

Contents lists available at ScienceDirect



Neurochemistry International

journal homepage: [www.elsevier.com/locate/neuint](http://www.elsevier.com/locate/neuint)



Blockade of the translocation and activation of c-Jun N-terminal kinase 3 (JNK3) attenuates dopaminergic neuronal damage in mouse model of Parkinson's disease

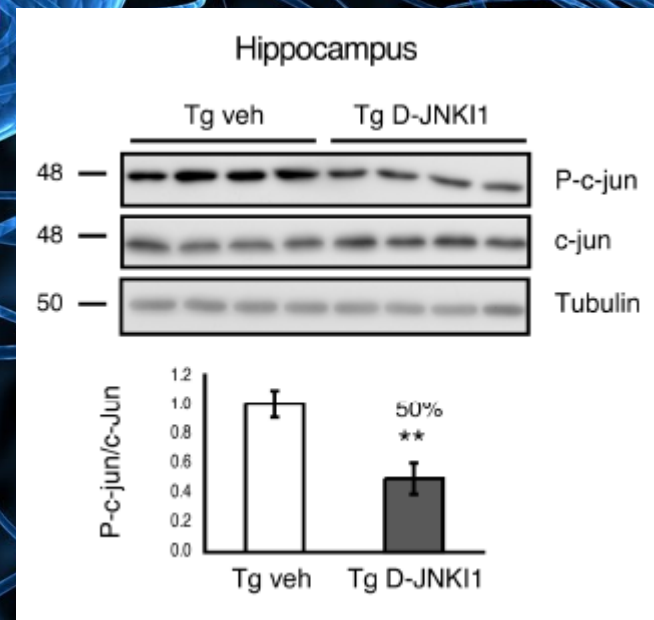
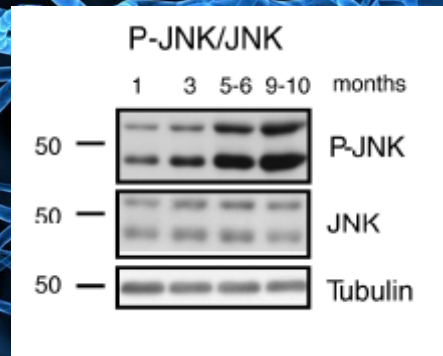
Jing Pan<sup>a,b</sup>, Qin Xiao<sup>a</sup>, Cheng-Yu Sheng<sup>b</sup>, Zhen Hong<sup>a</sup>, Hong-Qi Yang<sup>a</sup>, Gang Wang<sup>a</sup>, Jian-Qing Ding<sup>a,b,\*</sup>, Sheng-Di Chen<sup>a,b,\*</sup>

# IMPLICACIÓ DE JNK EN ALZHEIMER

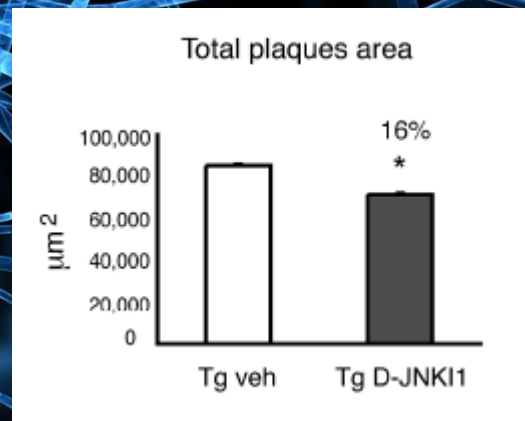
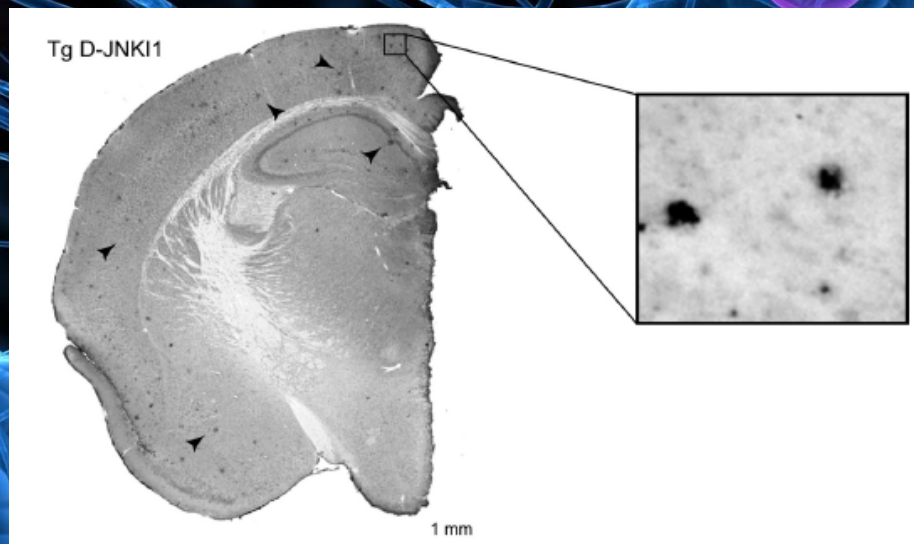
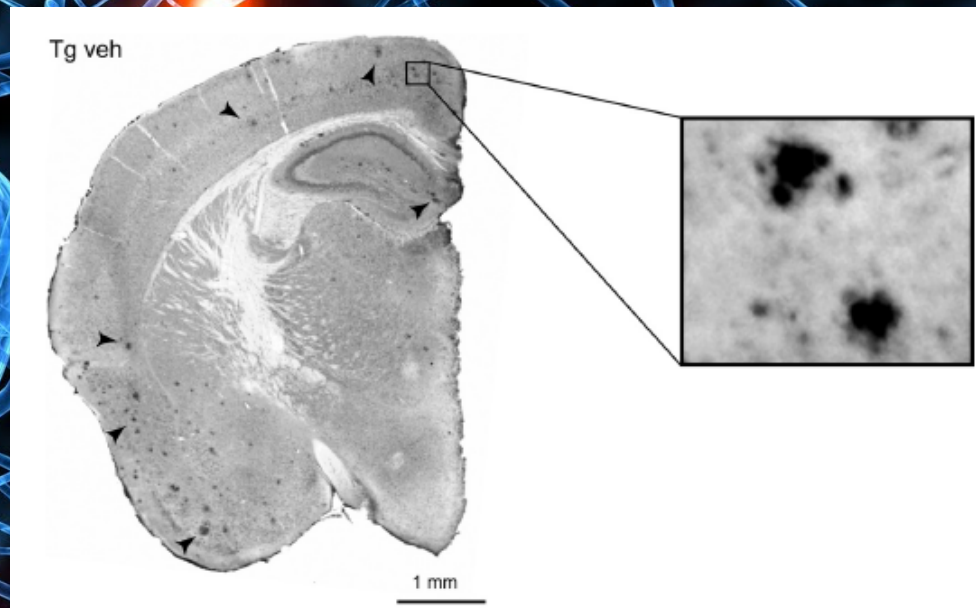
JBC Papers in Press. Published on October 27, 2011 as Manuscript M111.297515  
The latest version is at <http://www.jbc.org/cgi/doi/10.1074/jbc.M111.297515>

## c-Jun N-terminal Kinase regulates soluble A $\beta$ oligomers and cognitive impairment in an AD mouse model

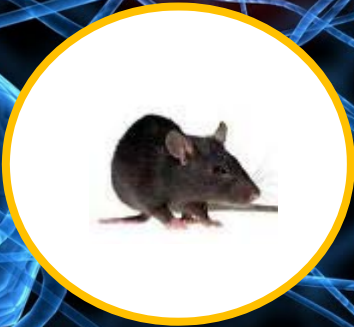
Alessandra Scip<sup>1\*</sup>, Xanthi Antoniou<sup>1\*</sup>, Alessio Colombo<sup>1</sup>, Giovanni Guido Camici<sup>2</sup>, Laura Pozzi<sup>1</sup>, Daniele Cardinetti<sup>1</sup>, Marco Feligioni<sup>1</sup>, Pietro Veglianesi<sup>1</sup>, Ferdinand H. Bahlmann<sup>3</sup>, Luigi Cervo<sup>1</sup>, Claudia Balducci<sup>1</sup>, Cinzia Costa<sup>3</sup>, Alessandro Tozzi<sup>3</sup>, Paolo Calabresi<sup>3,4</sup>, Gianluigi Forloni<sup>1</sup> & Tiziana Borsello<sup>1S</sup>



# IMPLICACIÓ DE JNK EN ALZHEIMER



# NOVEL RECOGNITION TEST



Fase d'habitució

24 hores

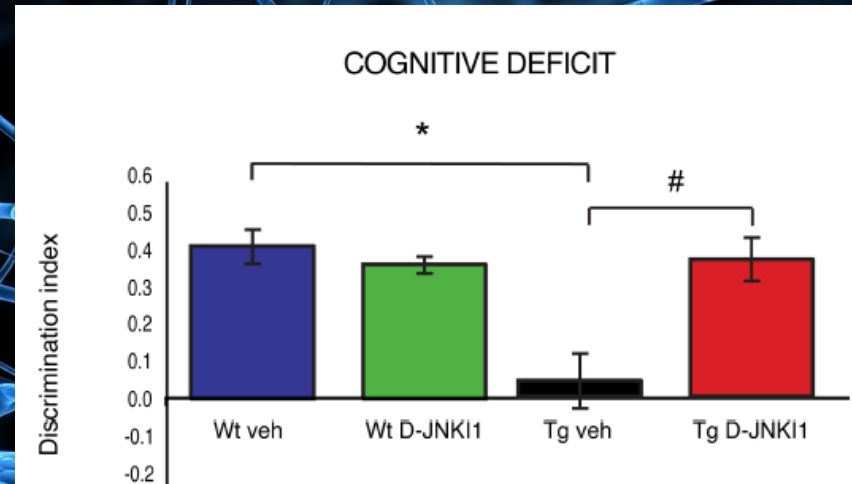


Fase d'exploració d'objectes

24 hores



Fase de reconeixement



Dedicació (temps)

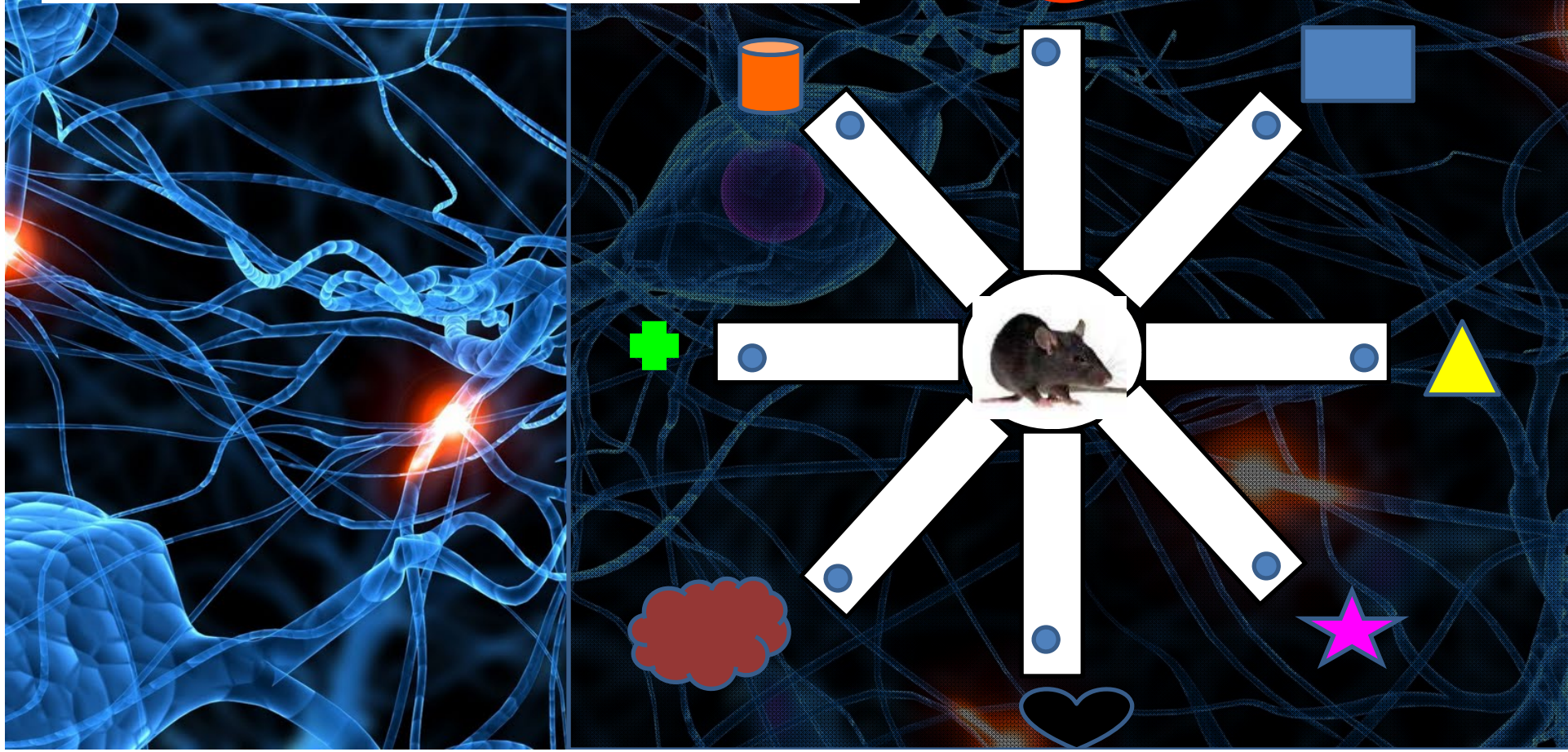
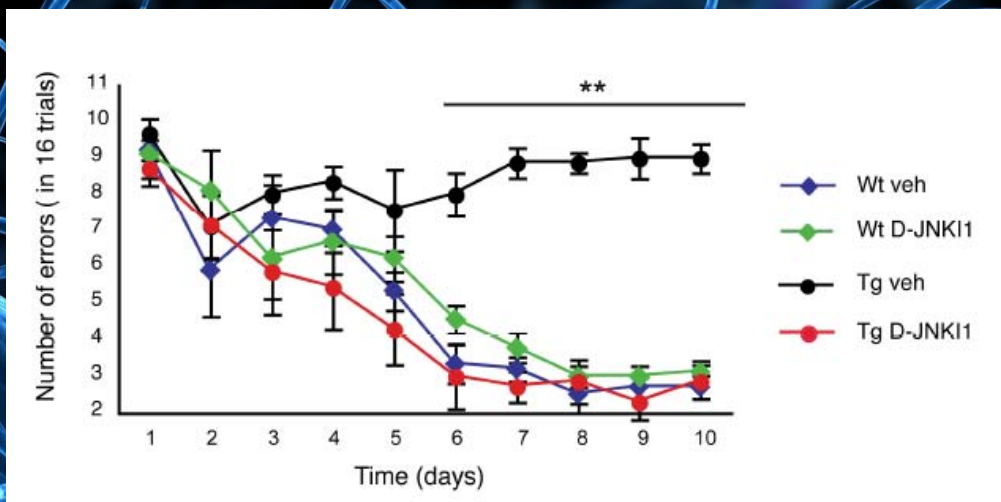
Ratolí sà



Ratolí transgènic







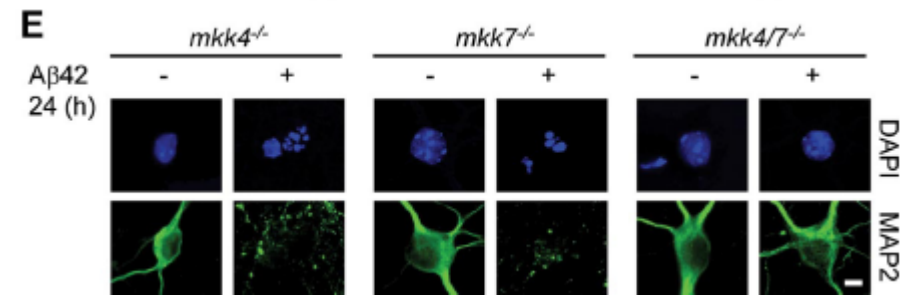
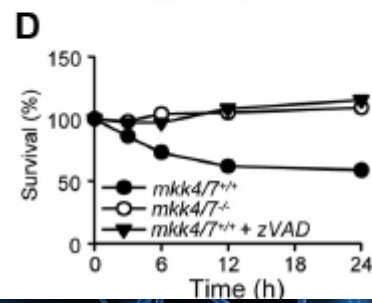
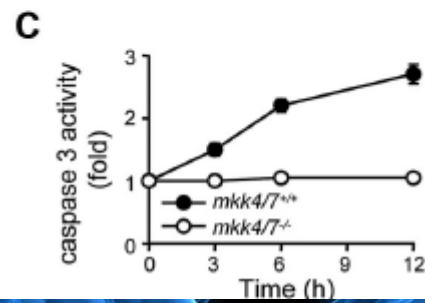
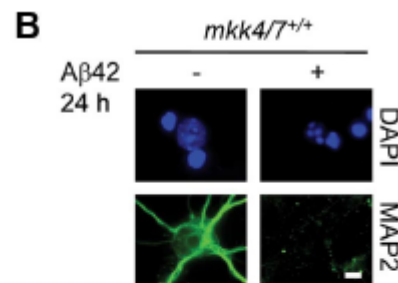
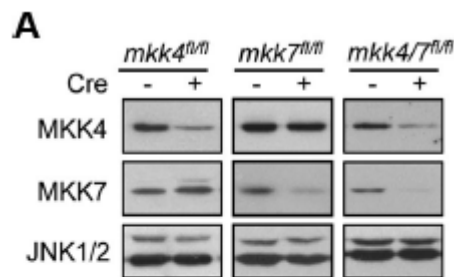
# IMPLICACIÓ DE JNK EN ALZHEIMER

The Journal of Neuroscience, November 23, 2011 • 31(47):16969–16976 • 16969

Cellular/Molecular

The Loss of c-Jun N-Terminal Protein Kinase Activity Prevents the Amyloidogenic Cleavage of Amyloid Precursor Protein and the Formation of Amyloid Plaques *In Vivo*

Sonia Mazzitelli,<sup>1</sup> Ping Xu,<sup>2</sup> Isidre Ferrer,<sup>3</sup> Roger J. Davis,<sup>2</sup> and Cathy Tournier<sup>1</sup>



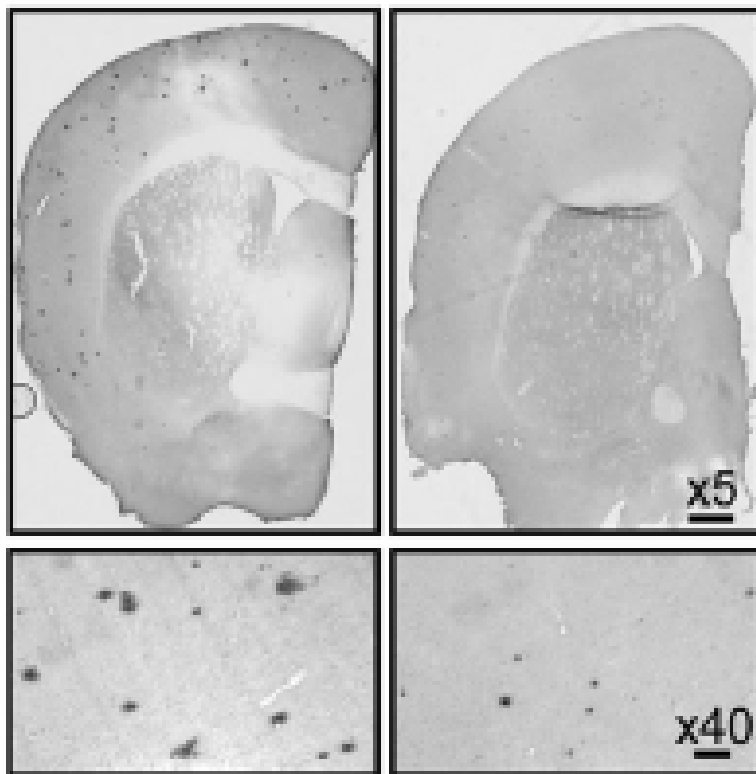
# IMPLICACIÓ DE JNK EN ALZHEIMER

**A**

*APP<sup>swe</sup>/PS1<sup>dE9</sup>*

*mkk4/7<sup>wt</sup>*

*mkk4/7<sup>Δbr</sup>*

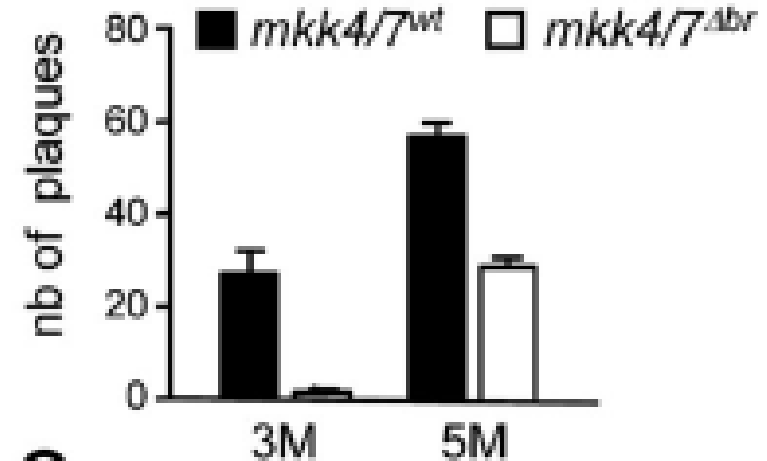


**B**

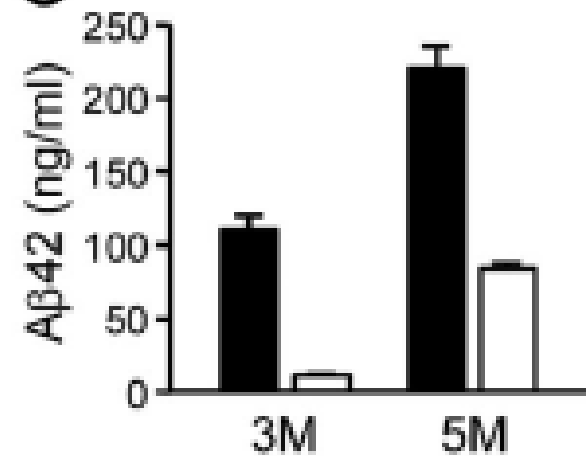
*APP<sup>swe</sup>/PS1<sup>dE9</sup>*


■ *mkk4/7<sup>wt</sup>*

□ *mkk4/7<sup>Δbr</sup>*



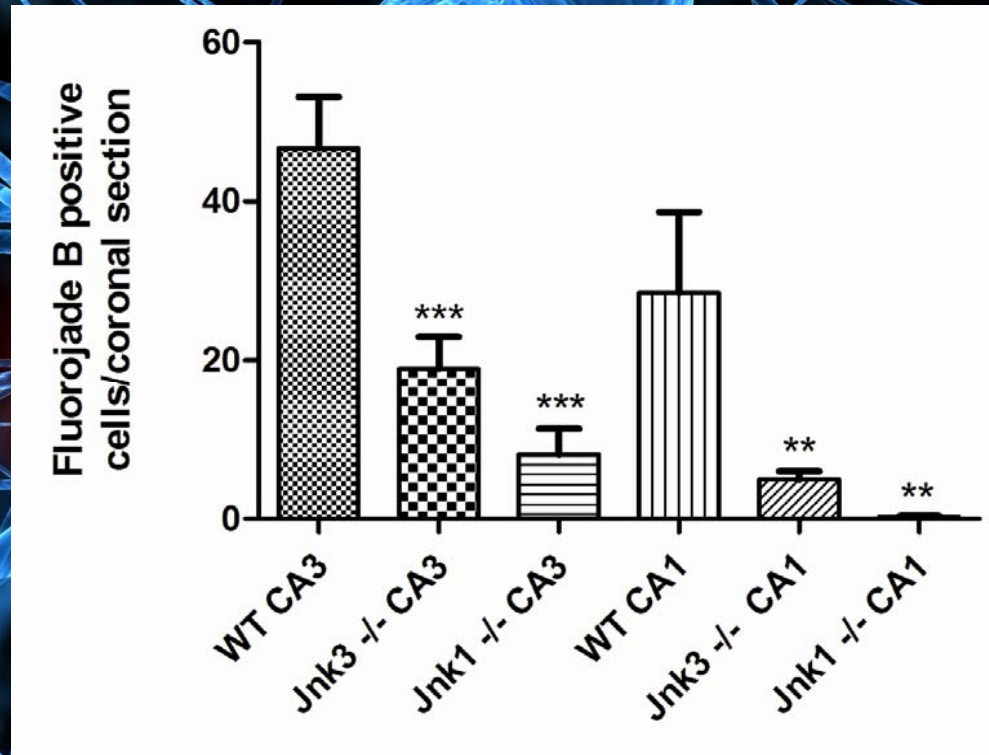
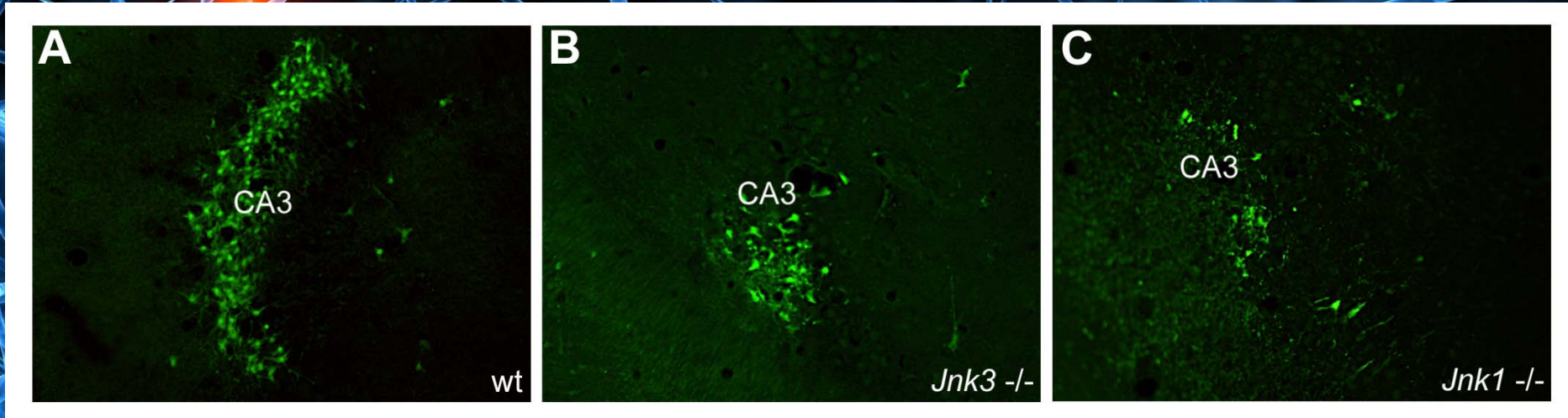
**C**





**CARACTERITZACIÓ DE LA FUNCIÓ DE  
JNK1 i JNK3 EN LA MORT PER  
EXCITOTOXICITAT**

# Reducció de la mort neuronal

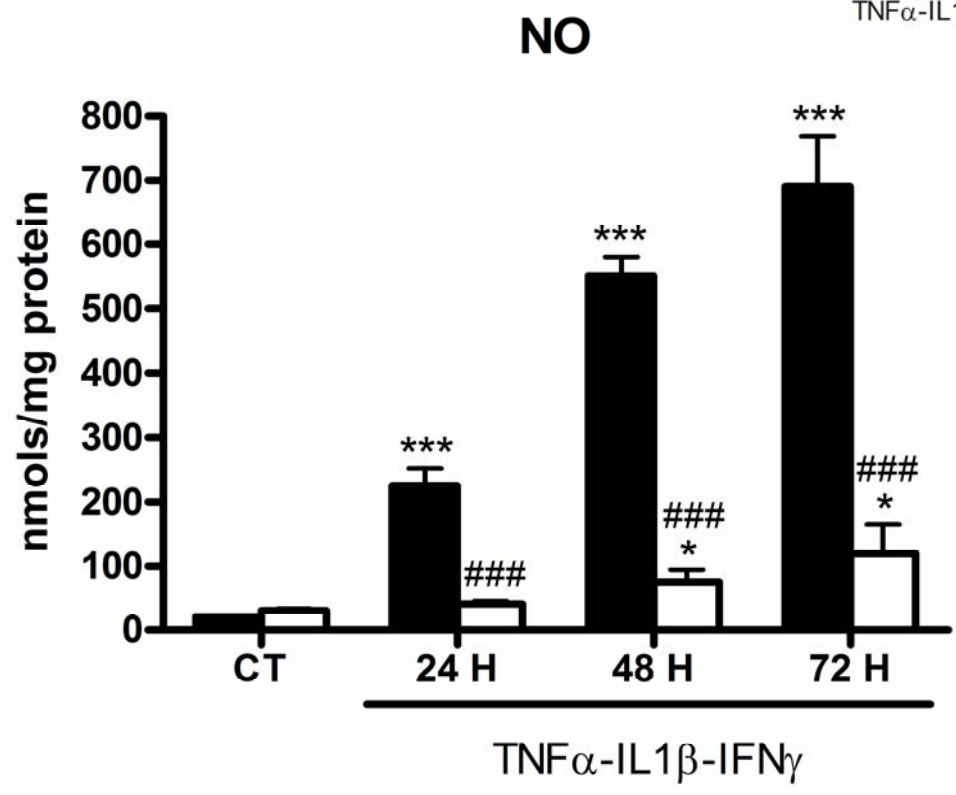
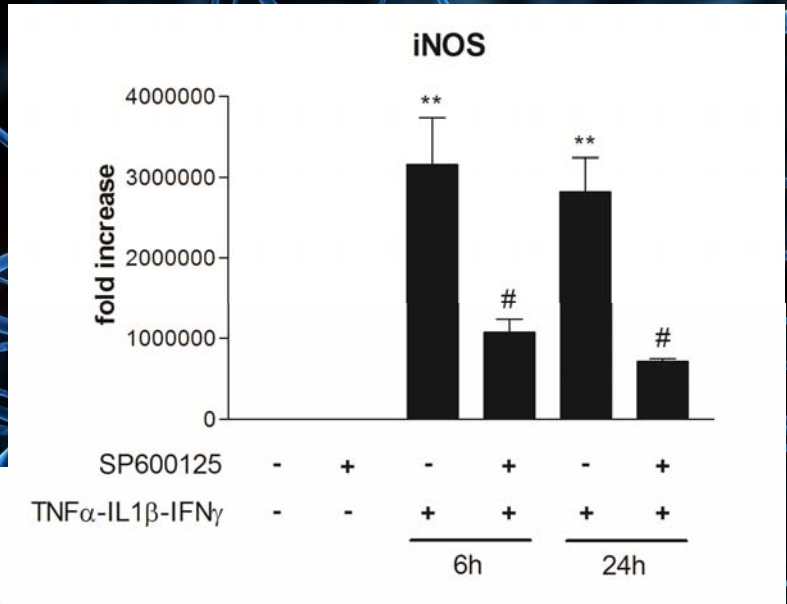
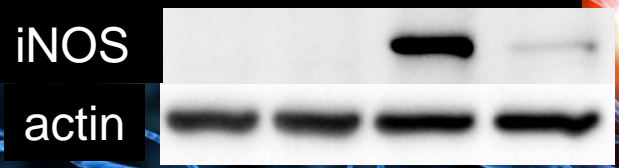


The background of the slide is a complex, abstract network of glowing blue lines and fibers, resembling a neural network or a web of connections. Several bright orange and red points of light are scattered throughout the network, suggesting active nodes or points of inflammation. The overall color palette is dominated by deep blues and oranges, creating a high-tech, scientific atmosphere.

# IMPLICACIÓ DE JNK EN LA NEUROINFLAMACIÓ

# IMPLICACIÓ DE JNK EN NEUROINFLAMACIÓ

	24 h			
TNF $\alpha$ -IL1 $\beta$ -IFN $\gamma$	-	-	+	+
SP600125	-	+	-	+



Wild-type (WT)  
 SP600125 treated WT

A 3D rendering of a complex neural network. The image features a dense web of glowing blue fibers, representing axons and dendrites, set against a dark blue background. Several bright orange and red light flares are scattered throughout the network, suggesting electrical activity or signal transmission. In the center of the network, a prominent, glowing purple sphere is visible, possibly representing a cell body or a specific node of interest. The overall aesthetic is futuristic and scientific.

**MOLTES GRÀCIES PER  
LA SEVA ATENCIÓ!!**