Le basi molecolari della neurodegenerazione

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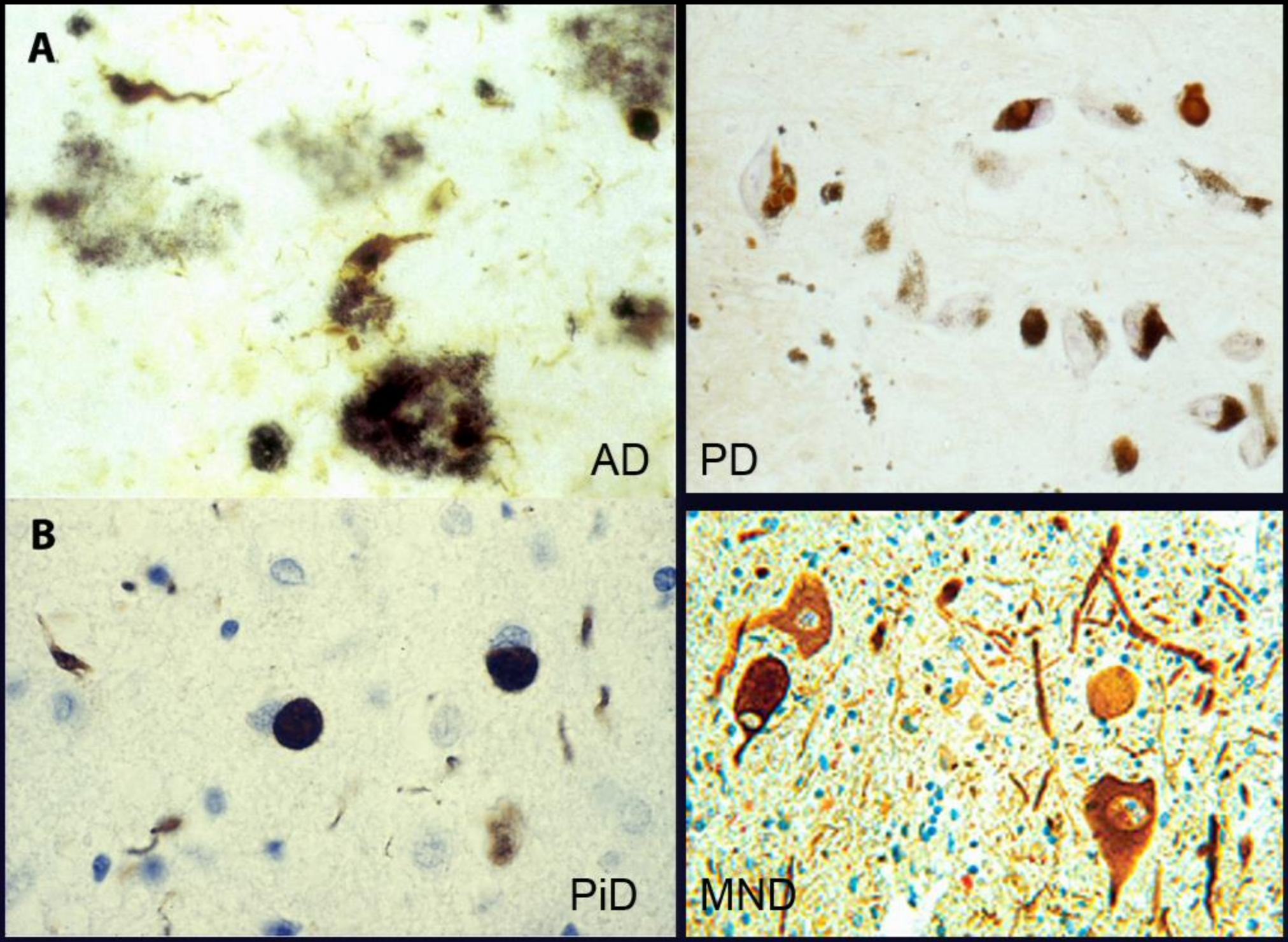
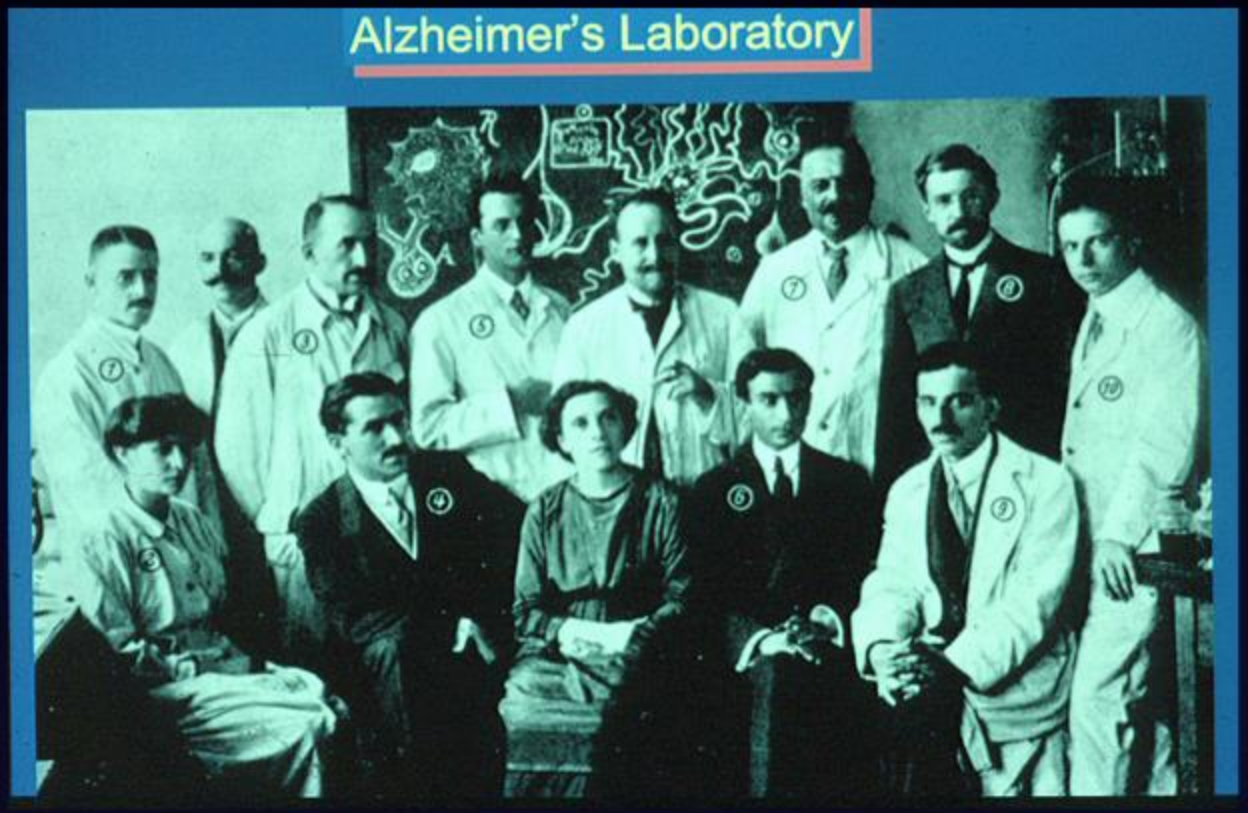
Department of Clinical Neurosciences
University of Cambridge


A
AD
PD
B
PiD
MND

Pytagora nel 6 secolo BC, Aristotele 4 secolo BC, scrivono che il declino della mente e' associato con l'eta' avanzata. Cicerone 1 secolo BC scrive che non tutti gli uomini con l'eta' perdono la memoria

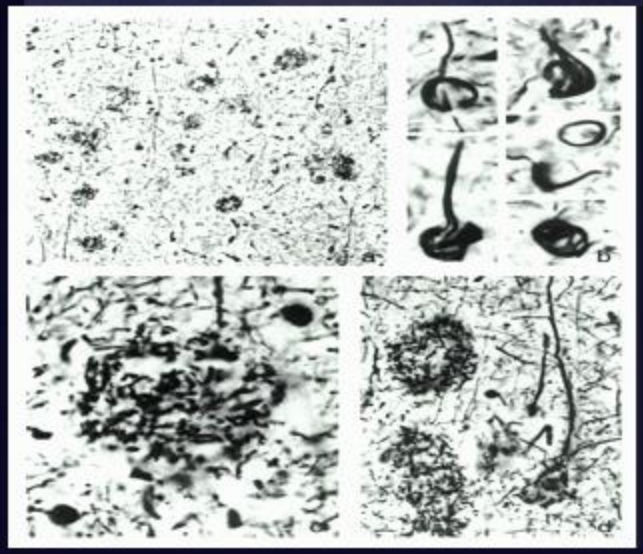
…..Ma forse piu' che l'attivita' fisica e' la decadenza delle capacita' mentali, che porta a dimenticare il nome degli schiavi, la faccia di un amico con cui hai cenato la sera prima o dei figli che hai generato e cresciuto……. ***Dalla Xth Satire D.G.Juvenal (I – II Century A.D.)***

Frequenza di malattie neurodegenerative a varie eta'- 7-10% > 65y; 30% > 80y; 50% > 85y



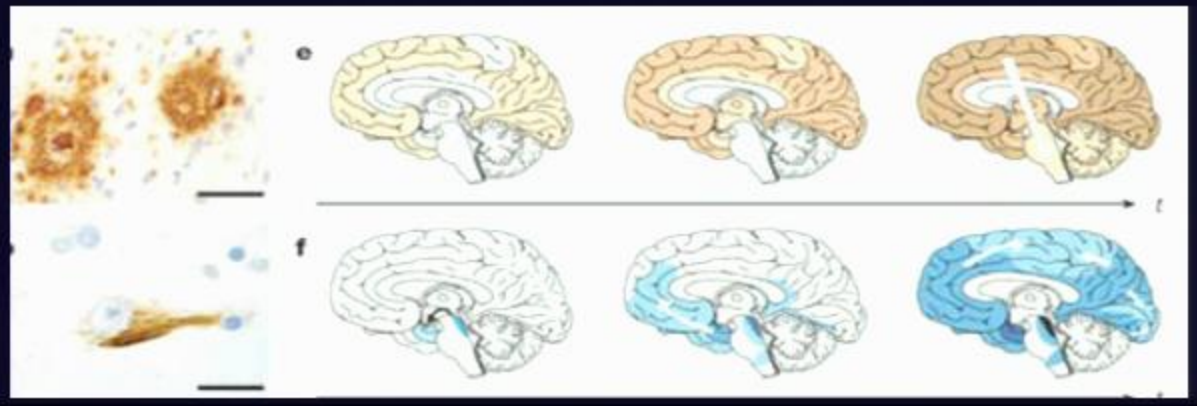
Nel mondo occidentale 40 milioni di persone sono affette da Alzheimer

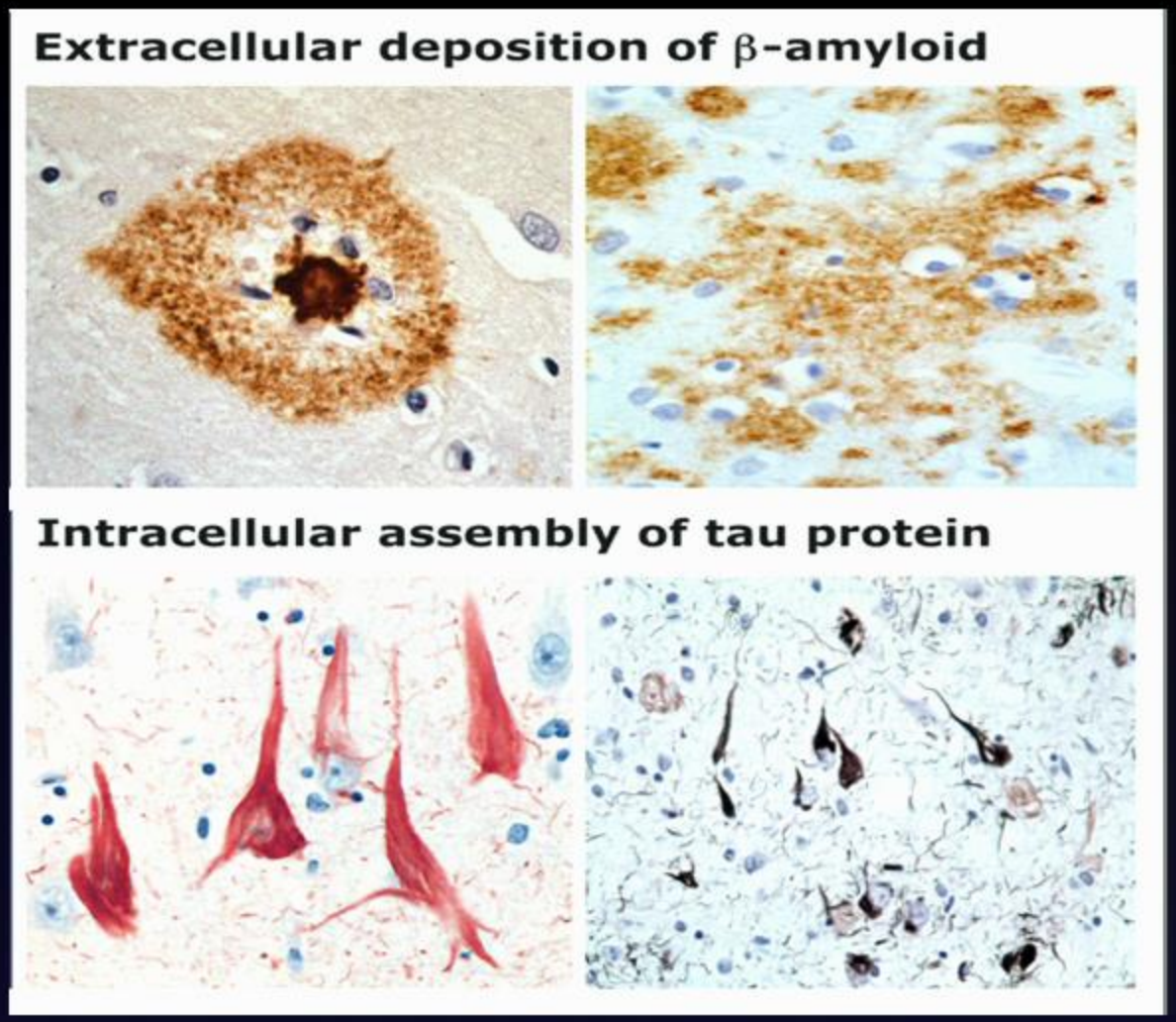
Patologia nel cervello di pazienti con Alzheimer



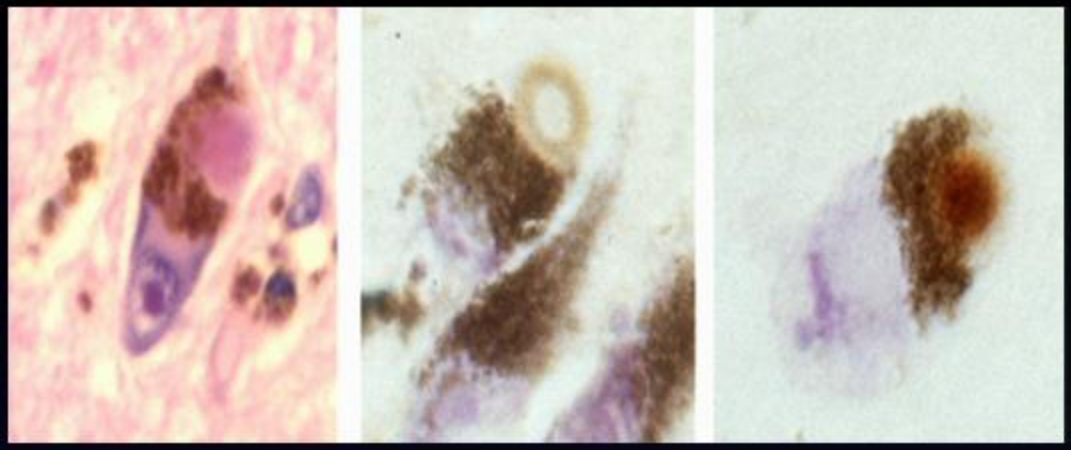
Aß

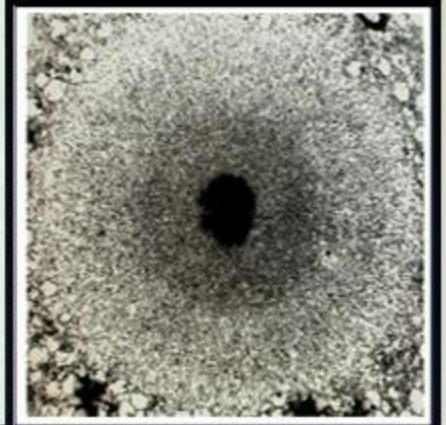
Tau

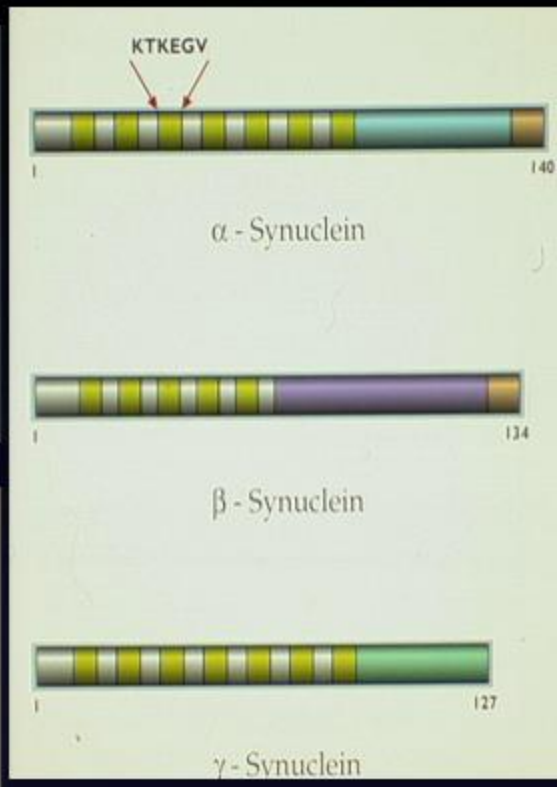




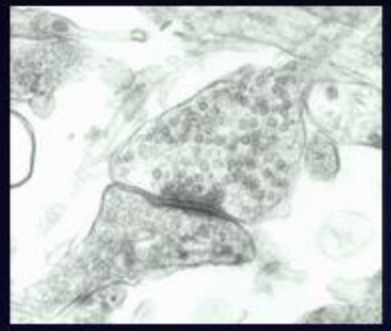
Lewy bodies e alpha-synuclein sono oltre che nel Parkinson anche in 50-60% di pazienti con Alzheimer

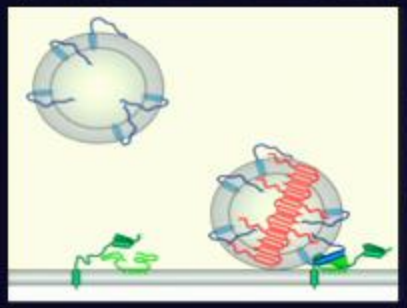


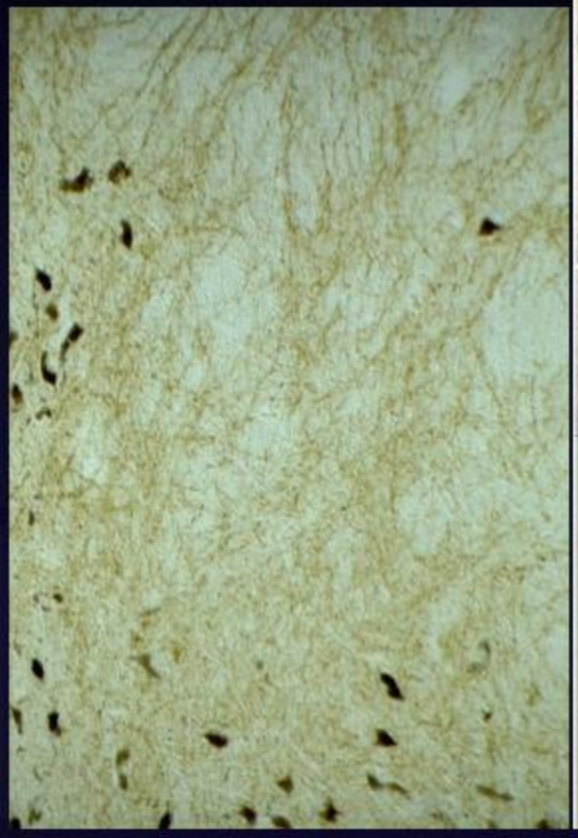


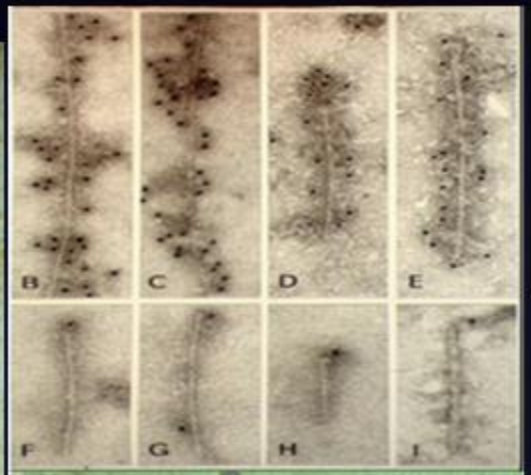


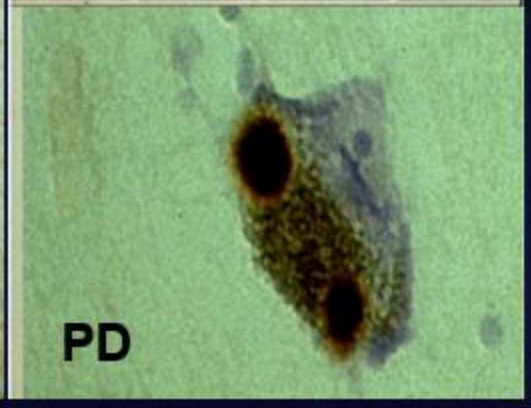
coinvolta nel rilascio di neurotransmet-titore

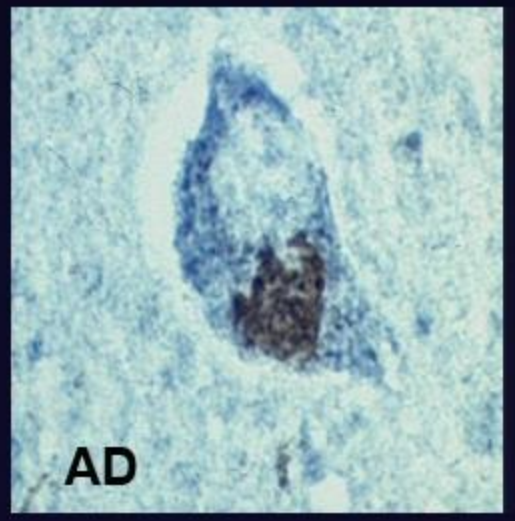


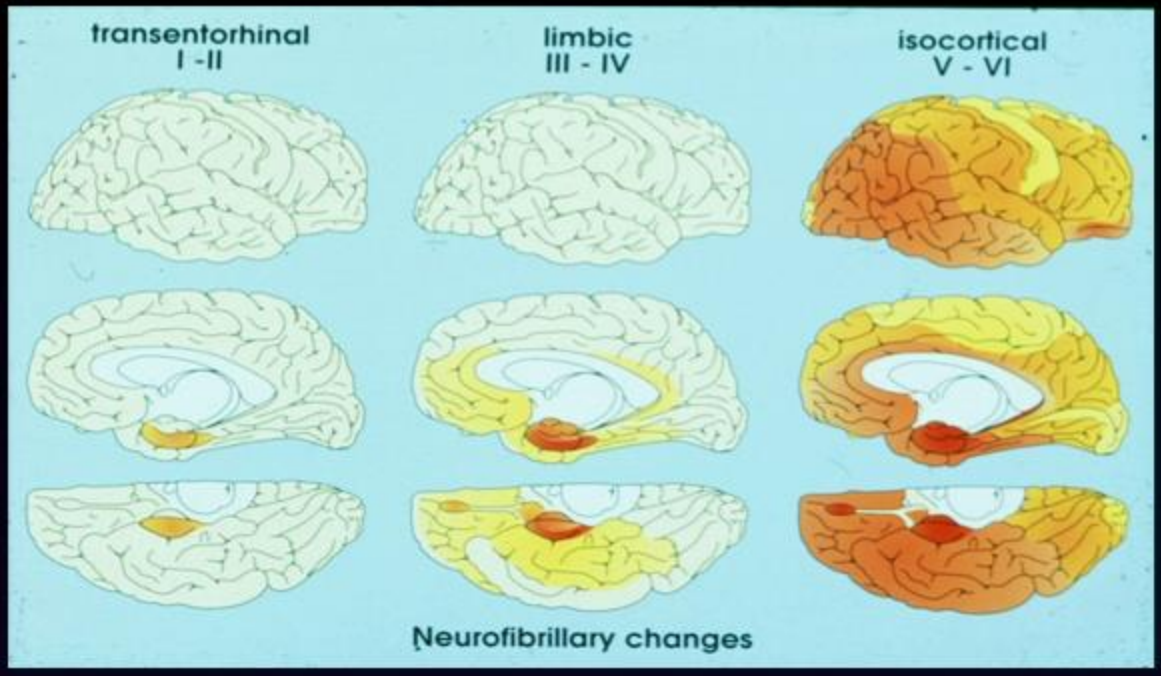




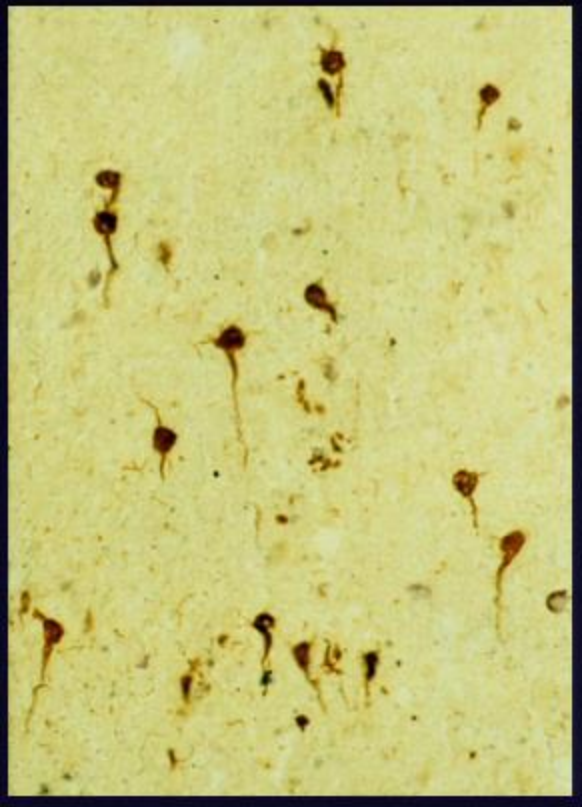


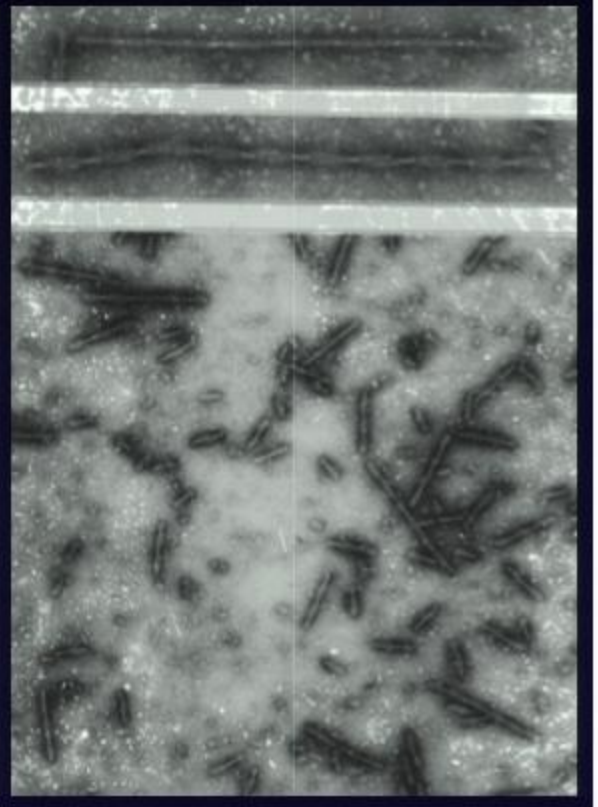


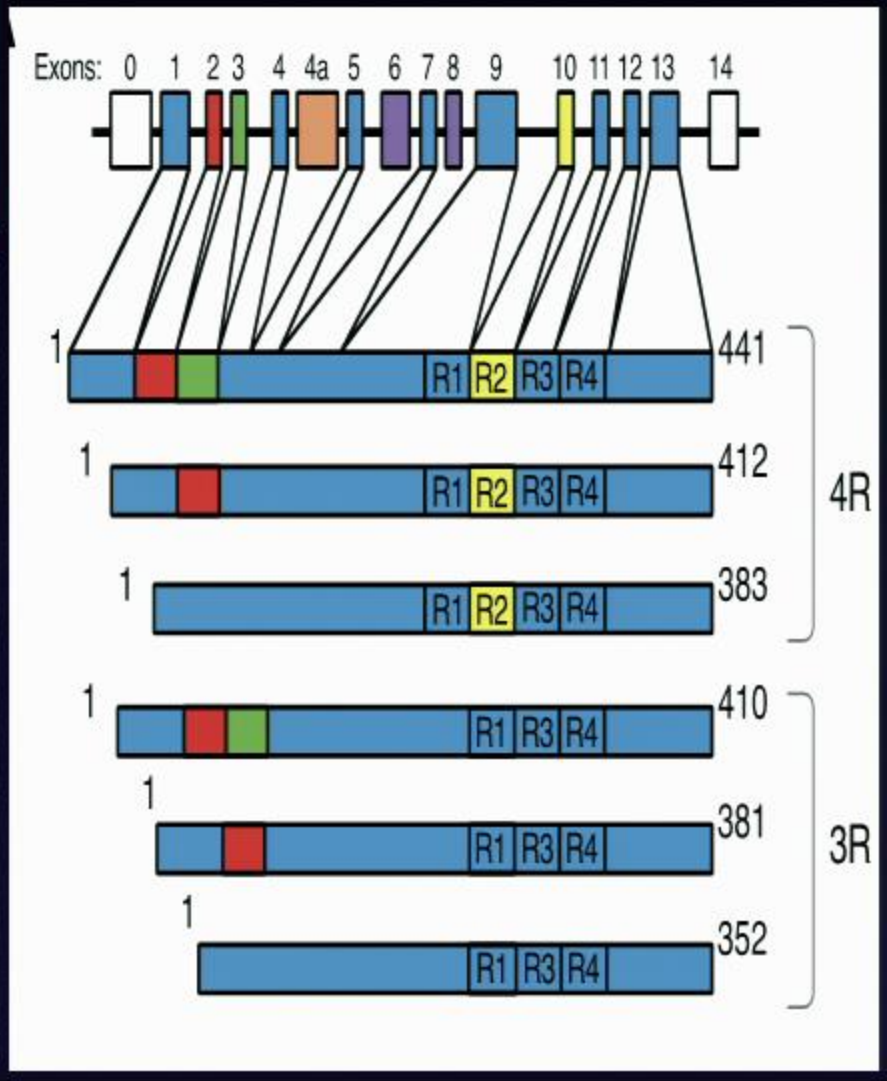




I filamenti negli aggregati Intracellulari (tangles) sono fatti di proteina tau (Goedert et al. 1988)







La tau si aggrega anche in altre malattie

Alzheimer's disease

Down's syndrome

Dementia Pugilistica

Pick's disease

FTDP-17

Only tangles dementia

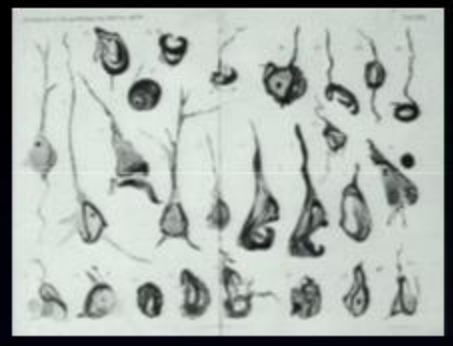
Progressive Supranuclear Palsy

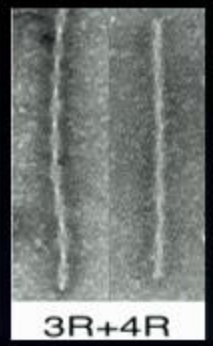
Corticobasal degeneration

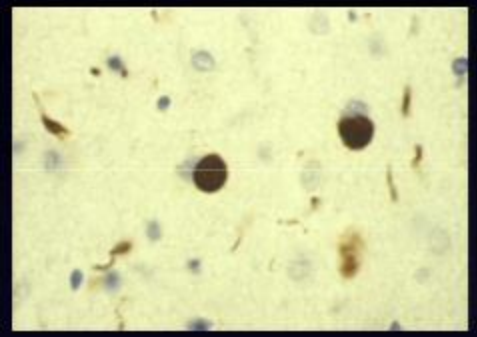
Argyrophilic grain disease

Parkinsonism and dementia complex of Guam

GSS with tangles

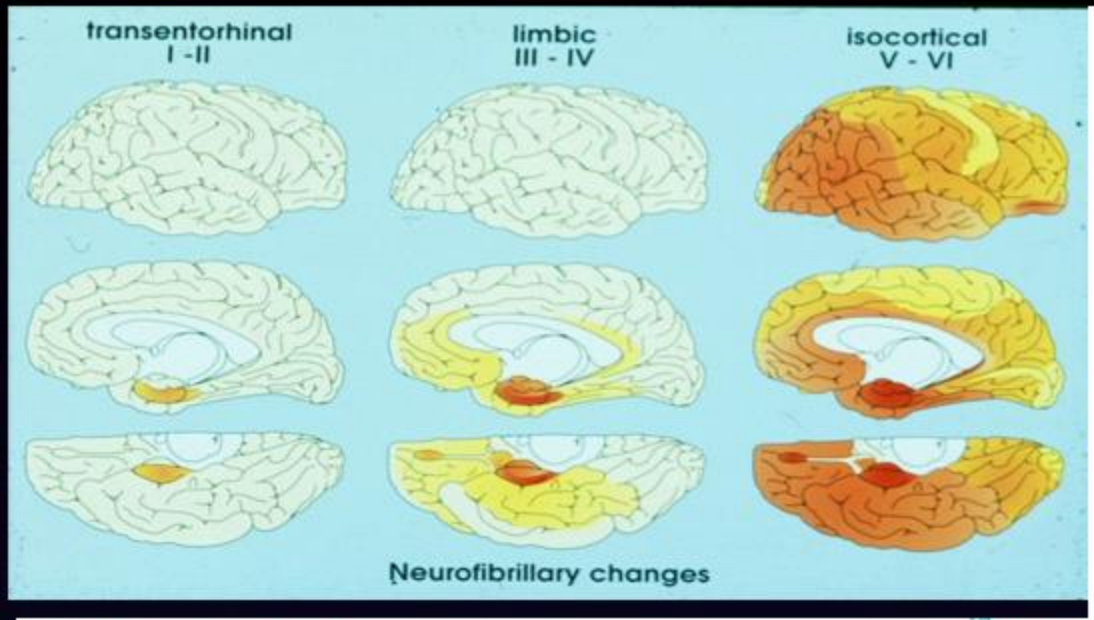






6 tau isoforms, 4R tau isoforms , 3R tau isoforms

Braak staging and spreading of tau pathology



Propagation of Tau Misfolding from the Outside to the Inside of a Cell*

Bess Frost[‡§], Rachel L. Jacks[‡§], and Marc I. Diamond[‡§¶]

From the Departments of [‡]Neurology and [¶]Cellular and Molecular Pharmacology and [§]Biomedical Sciences Program, University of California, San Francisco, California 94143

J Biol Chem 284, 12845-12852 (2009)

Transmission and spreading of tauopathy in transgenic mouse brain

Florence Clavaguera, Tristan Bolmont, R. Anthony Crowther, Dorothee Abramowski, Stephan Frank,Alphonse Probst1, Graham Fraser, Anna K. Stalder, Martin Beibel, Matthias Staufenbiel, Mathias Jucker, Michel Goedert, and Markus Tolnay

nature cell biology VOLUME 11 | NUMBER 7 | JULY 2009

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Trans-Synaptic Spread of Tau Pathology *In Vivo*

Li Liu[1], Valerie Drouet[1], Jessica W. Wu[1], Menno P. Witter[2], Scott A. Small[3], Catherine Clelland[1], Karen Duff[1,4]*

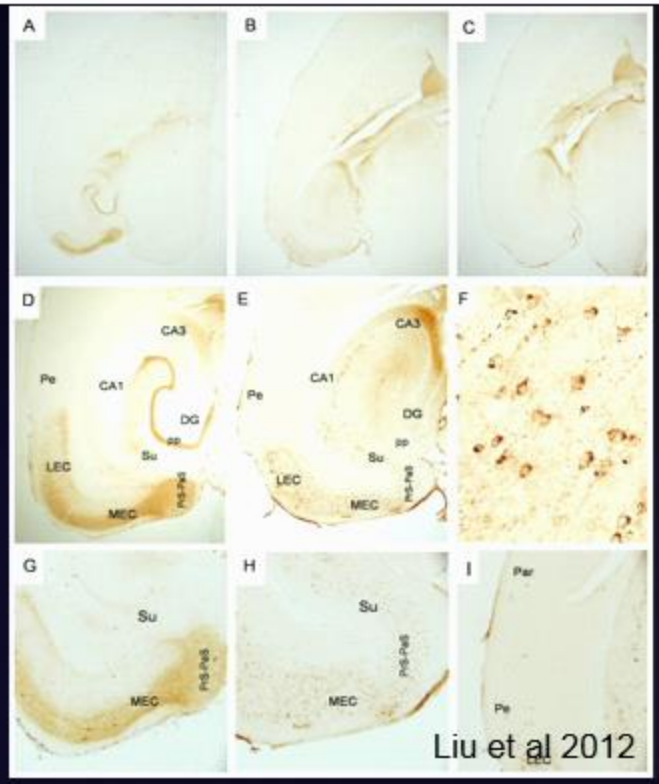
1 Department of Pathology and Cell Biology, Taub Institute for Alzheimer's Disease Research, Columbia University, New York, New York, United States of America, 2 Kavli Institute for Systems Neuroscience and Centre for the Biology of Memory, Norwegian University of Science and Technology, Trondheim, Norway, 3 Department of Neurology, Taub Institute for Alzheimer's Disease Research, Columbia University, New York, New York, United States of America, 4 Department of Psychiatry, New York

Neuron
Article

Propagation of Tau Pathology in a Model of Early Alzheimer's Disease

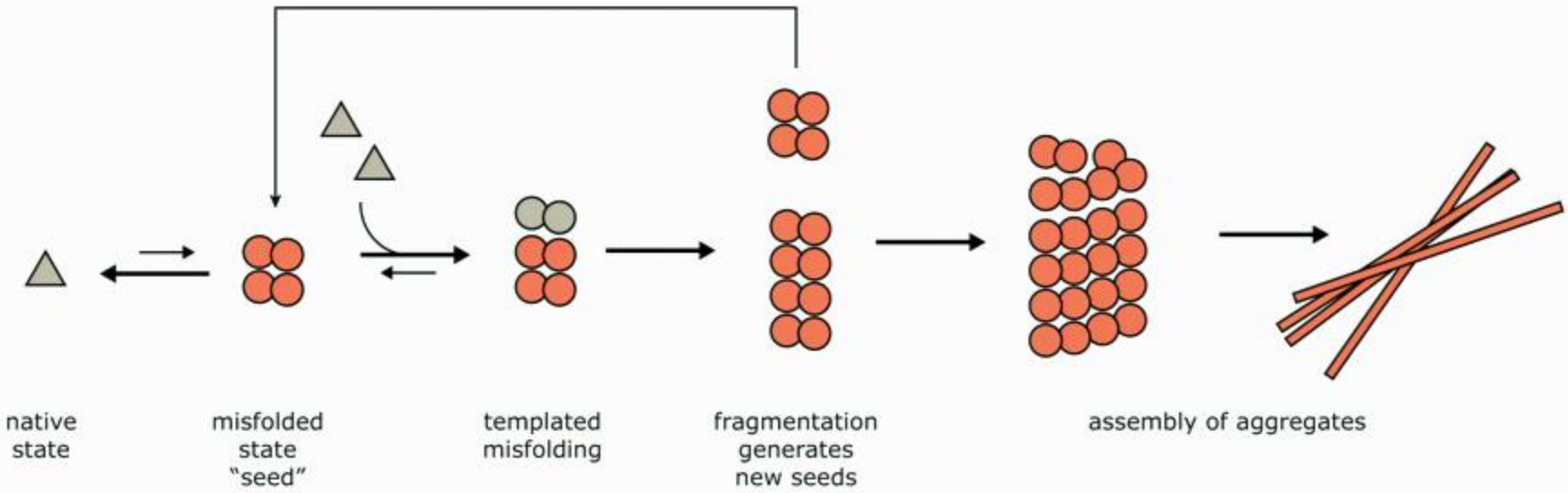
Alix de Calignon,[1,2,8] Manuela Polydoro,[1,8] Marc Suárez-Calvet,[1,3] Christopher William,[1] David H. Adamowicz,[1] Kathy J. Kopeikina,[1,4] Rose Pitstick,[5] Naruhiko Sahara,[6] Karen H. Ashe,[7] George A. Carlson,[5] Tara L. Spires-Jones,[1] and Bradley T. Hyman[1,*]

[1]MassGeneral Institute for Neurodegenerative Disease, Department of Neurology, Alzheimer's Disease Research Laboratory, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA
[2]Department of Physiology, Anatomy, and Genetics, University of Oxford, Oxford OX1 3QX, UK
[3]Department of Neurology, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona 08025, Spain
[4]Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, MA 02118, USA
[5]McLaughlin Research Institute, Great Falls, MT 59405, USA



Liu et al 2012

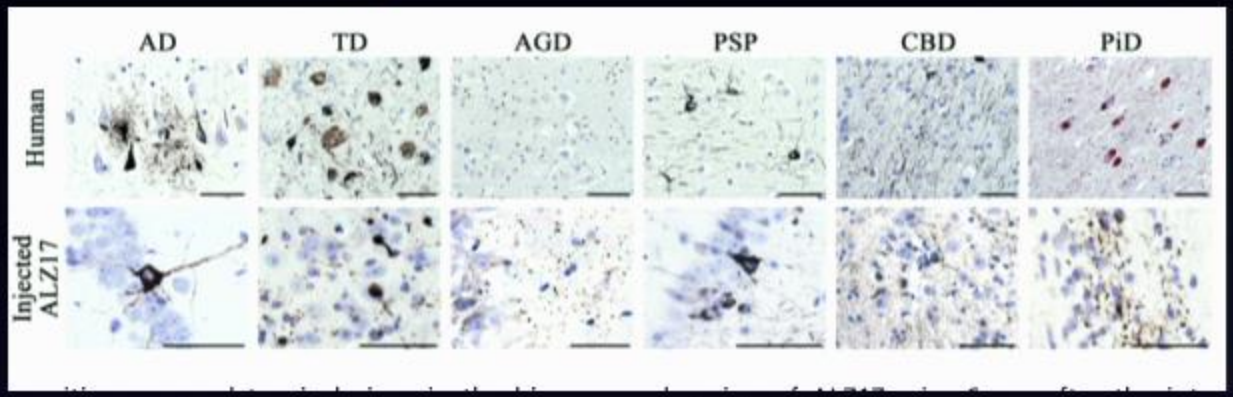
Protein misfolding through nucleation-dependent seeding

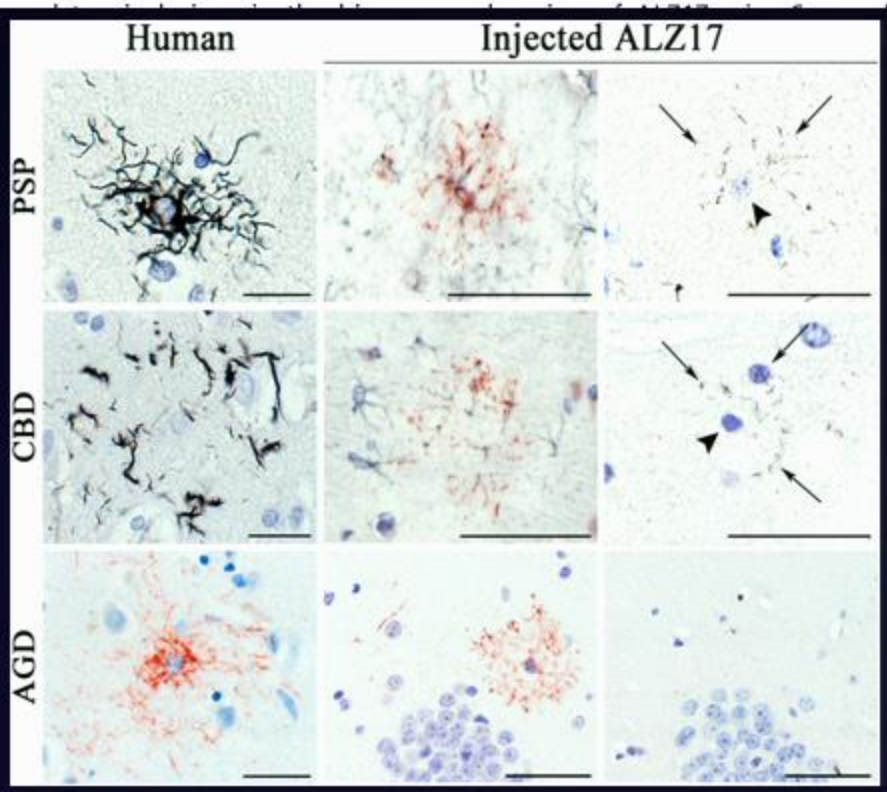


Brain homogenates from human tauopathies induce tau inclusions in mouse brain

Florence Clavaguera[a], Hiroyasu Akatsu[b], Graham Fraser[c], R. Anthony Crowther[c], Stephan Frank[a], Jürgen Hench[a], Alphonse Probst[a], David T. Winkler[a,d], Julia Reichwald[e], Matthias Staufenbiel[e], Bernardino Ghetti[f], Michel Goedert[c,1,2], and Markus Tolnay[a,1,2]

[a]Department of Neuropathology, Institute of Pathology, University Hospital, 4031 Basel, Switzerland; [b]Choju Medical Institute, Fukushimura Hospital, Toyohashi City 441-8124, Japan; [c]Medical Research Council Laboratory of Molecular Biology, Cambridge CB2 0QH, United Kingdom; [d]Department of Neurology, University Hospital, 4031 Basel, Switzerland; [e]Novartis Institutes for Biomedical Research, 4056 Basel, Switzerland; and [f]Indiana Alzheimer Disease Center and Department of Pathology and Laboratory Medicine, Indiana University, Indianapolis, IN 46202





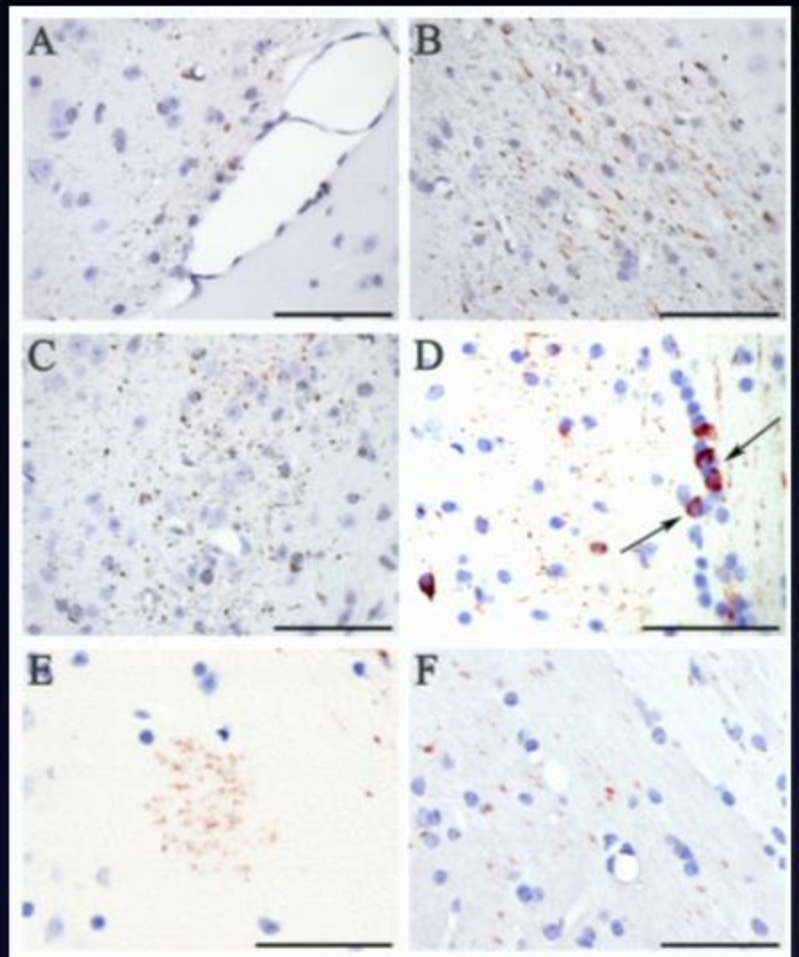
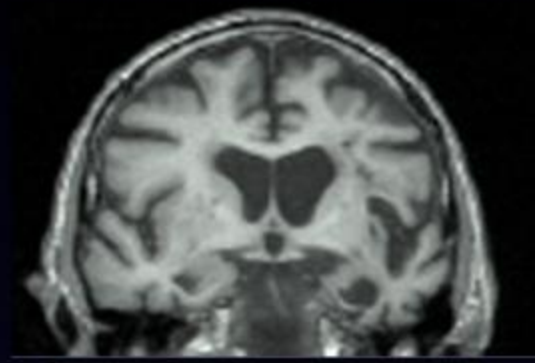


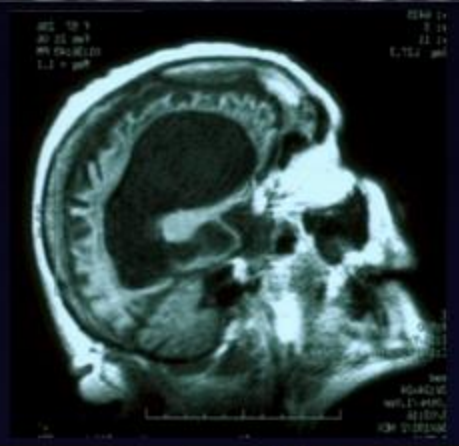
Fig. 3. Induction of tau inclusions in nontransgenic C57BL/6 mice 12 mo after the intracerebral injection of brain homogenates from sporadic human tauopathies. Gallyas-Braak silver impregnation revealed the presence of neuropil threads and coiled bodies in (*A*) the optic tract following the in

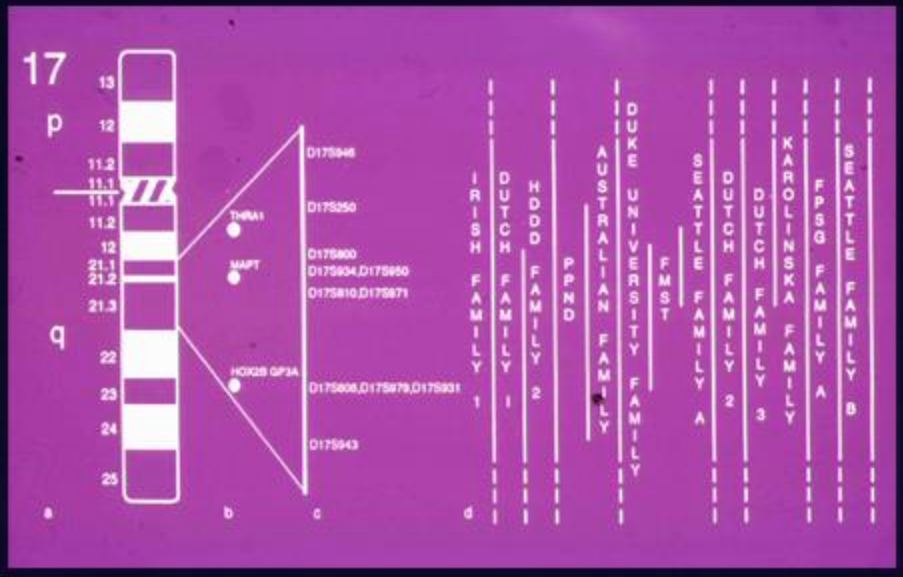
Demenza frontotemporale

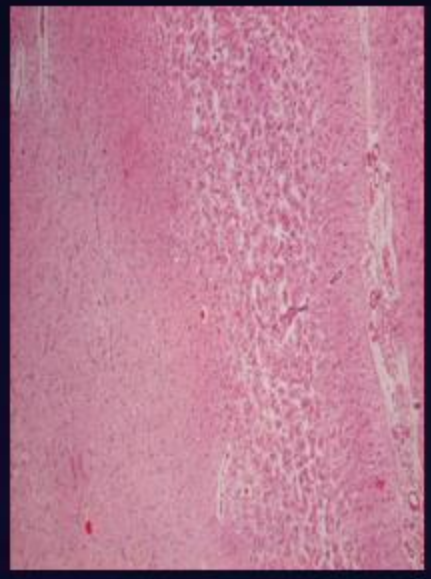
Alterazioni comportamentali e tardo declino cognitivo

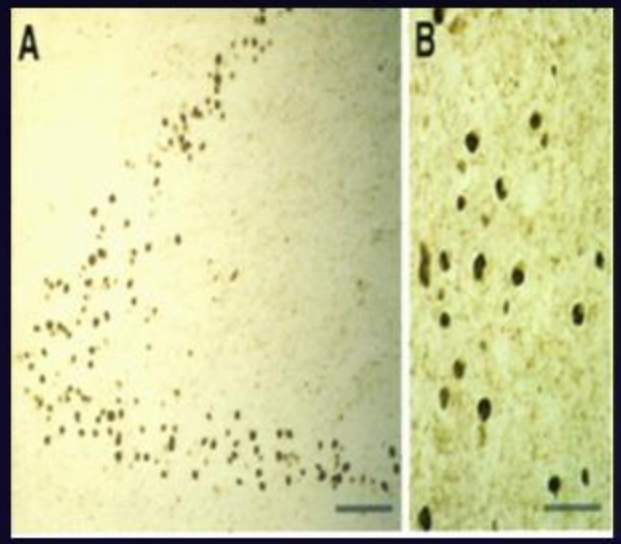
Arnold Pick 1892



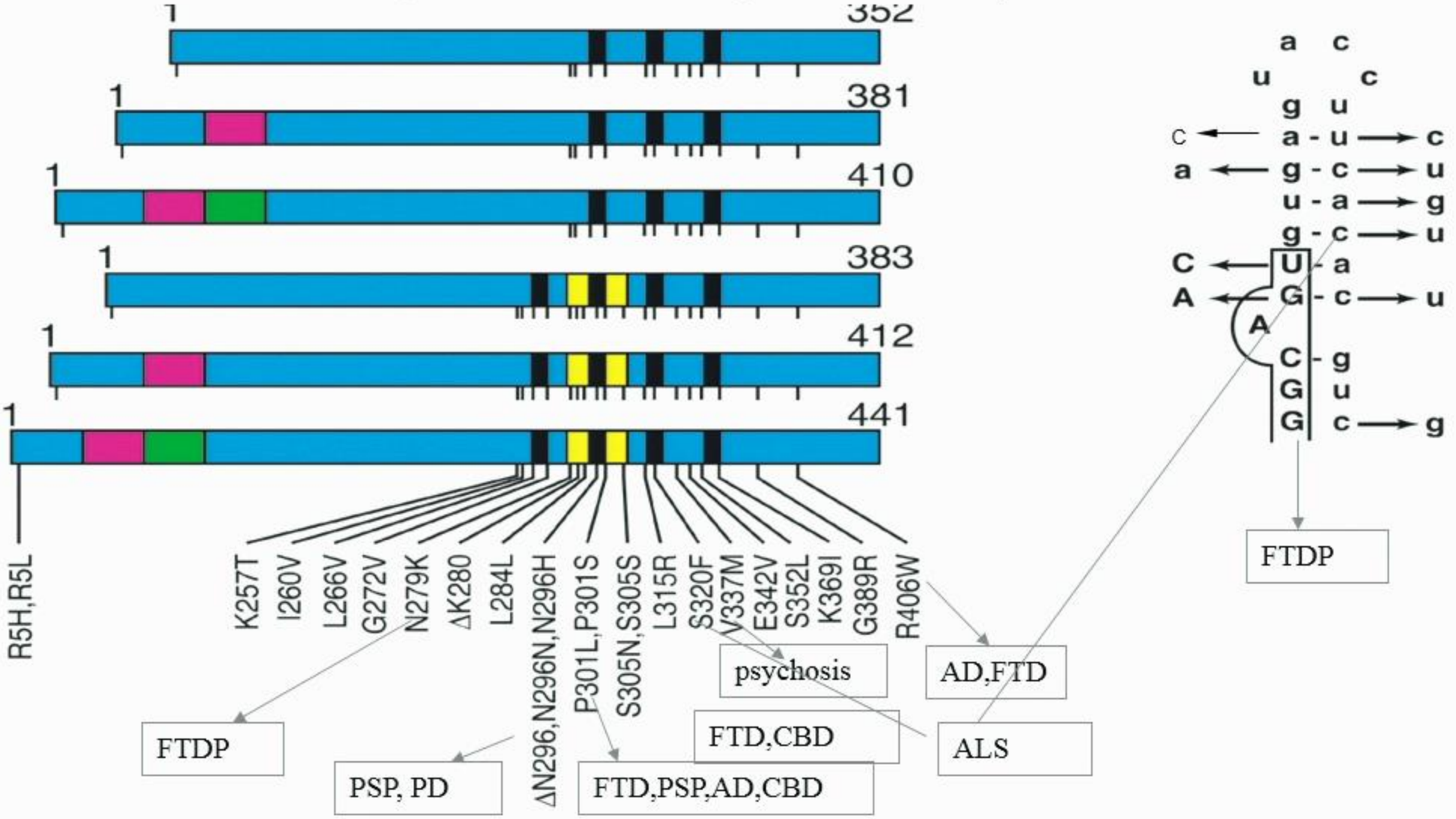








Mutazioni genetiche nel gene della proteina tau



-Change the ratio of tau isoform expression (mainly increase of tau with 4 repeats but +4/-15 increase of 3 repeats)

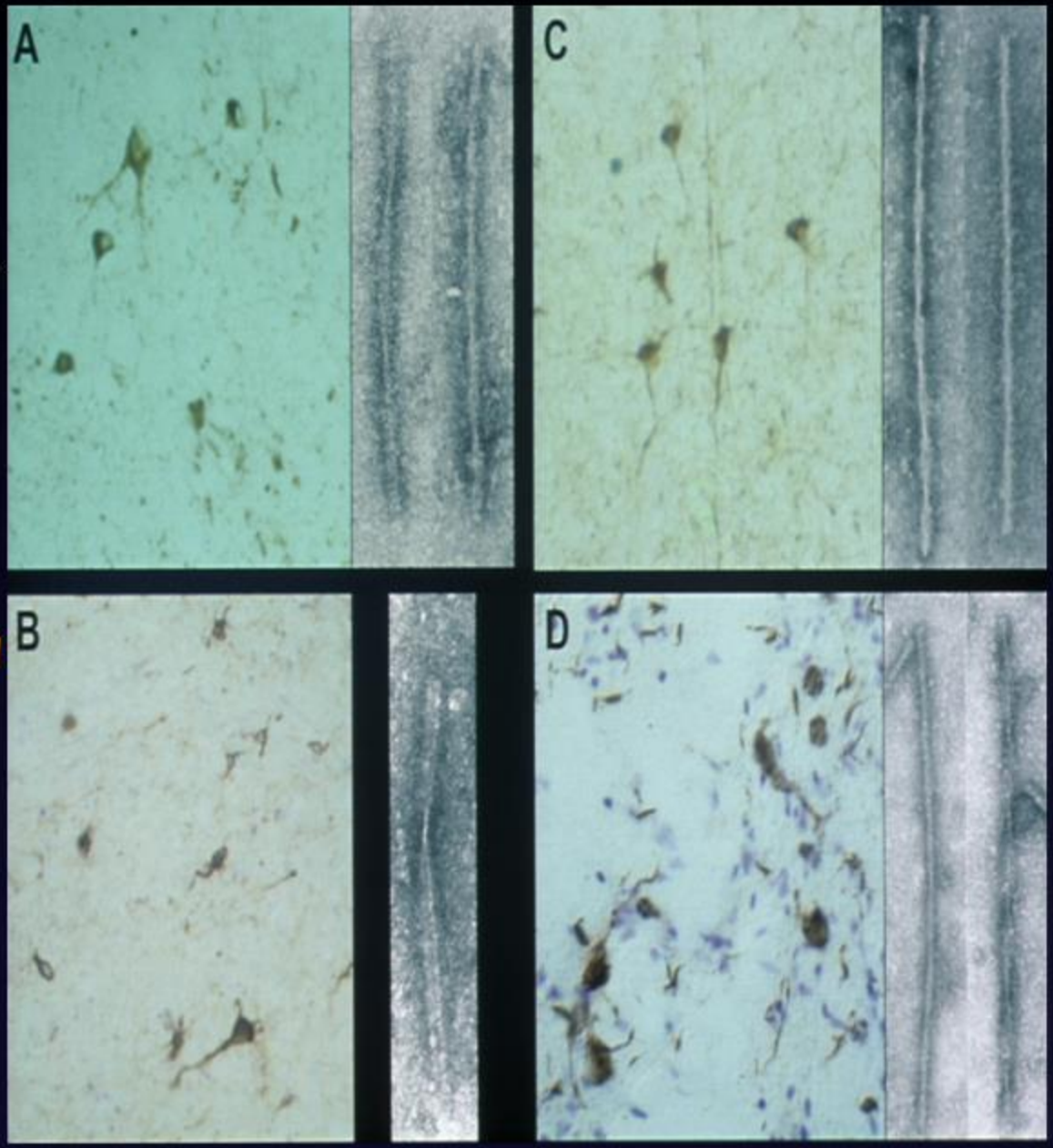
-Reduce ability of tau to bind to microtubules

-Lead to specific tau isoform aggregation

-Disrupt binding to dynactin

FTDP-17T tau pathology is similar to sporadic tauopathies

P301L
Tau pathology resembles that of PSP

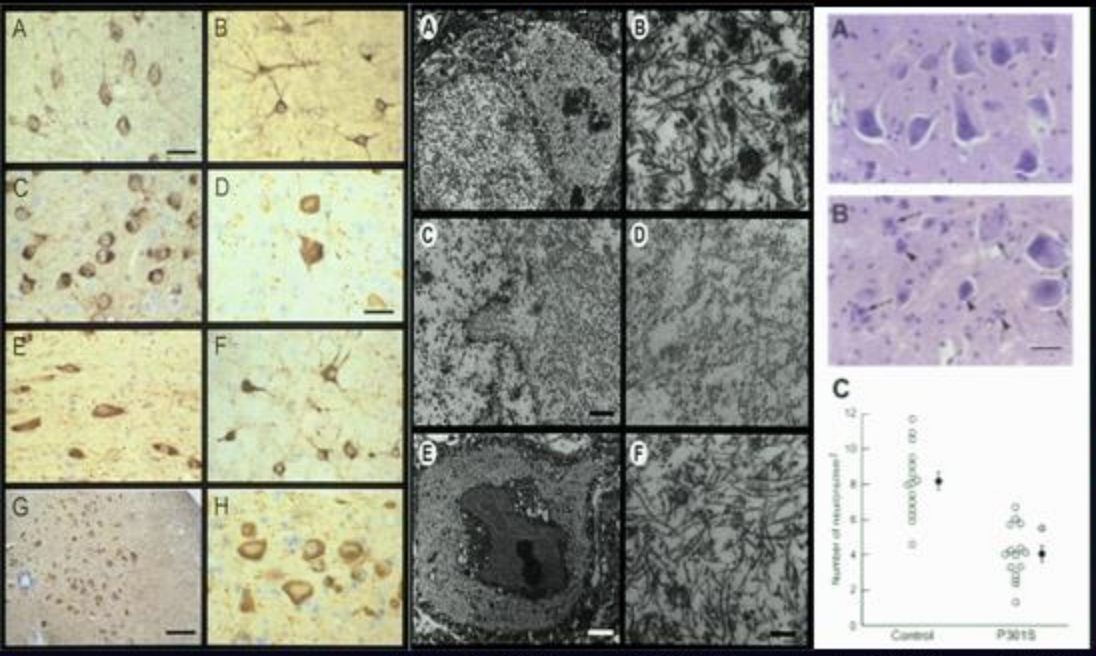


V337M
Tau pathology resembles that of AD

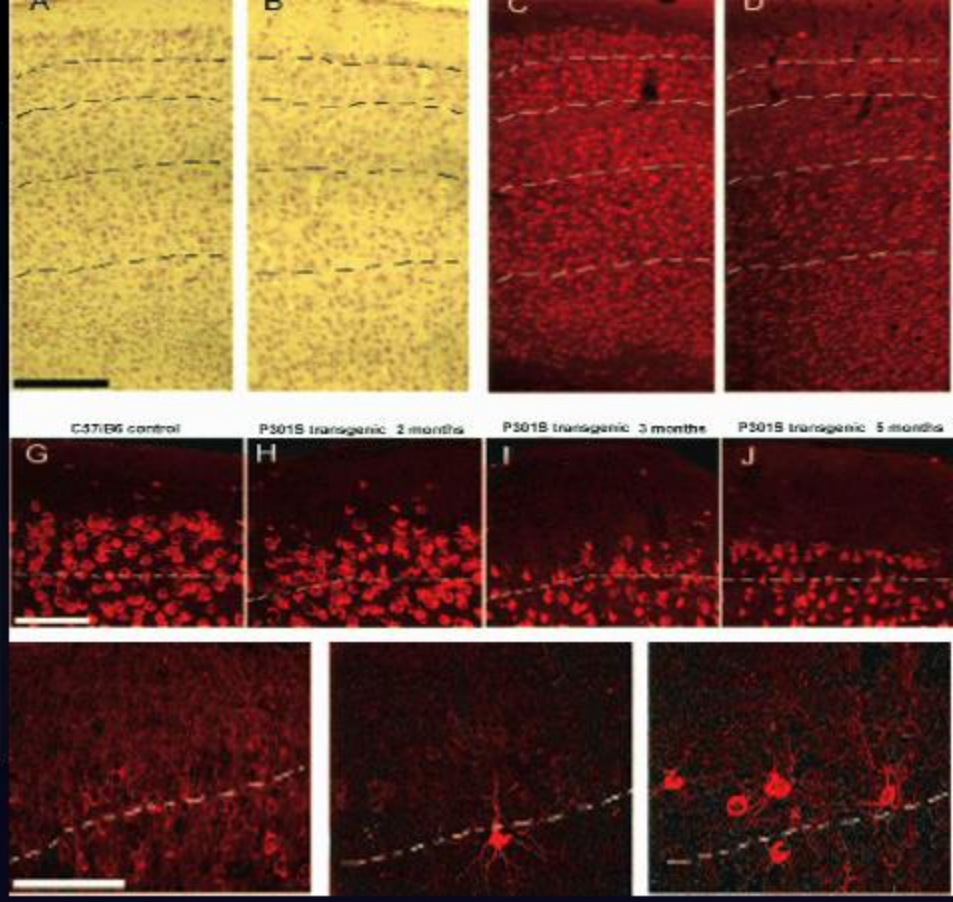
Intron following exon 10.
Tau pathology resembles that of CBD

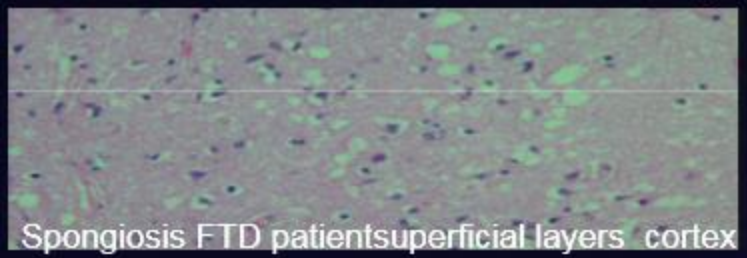
G389R
Tau pathology resembles that of PiD

mThy1.2 promoter | P301S *tau* cDNA



Allen et al. J Neurosci 2002; Hampton et al. J Neurosci 2010

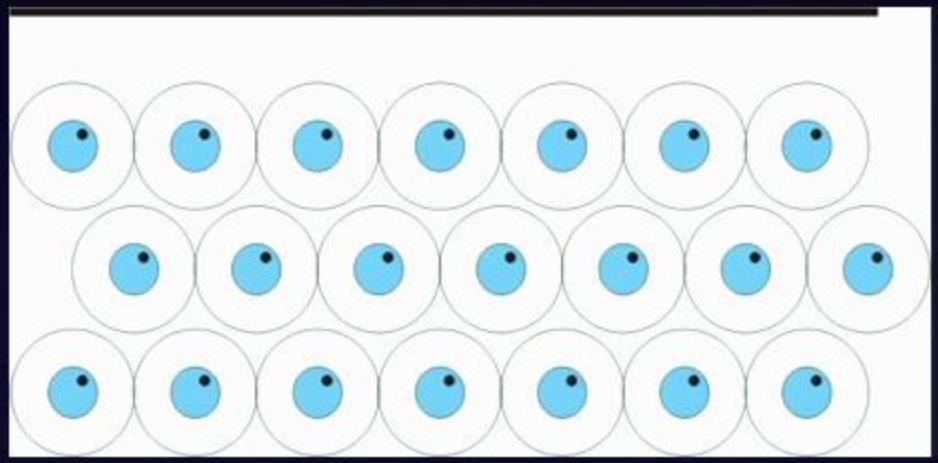




Spongiosis FTD patientsuperficial layers cortex

In P301S tau transgenic mice tau deposits and filaments are present at 5 w and their amount increases up to 4-5 months causing a progressive motor phenotype for which the mice have to be culled at the age of 5-6 months.

FTDP Tau patient cortex



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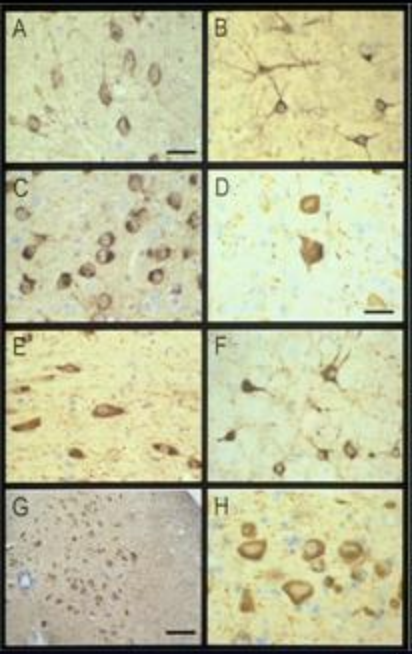
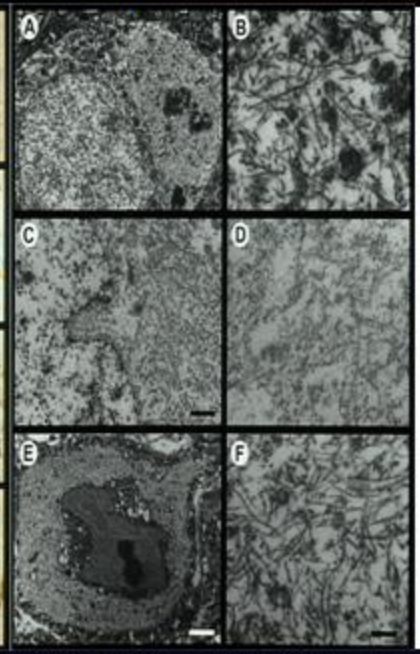
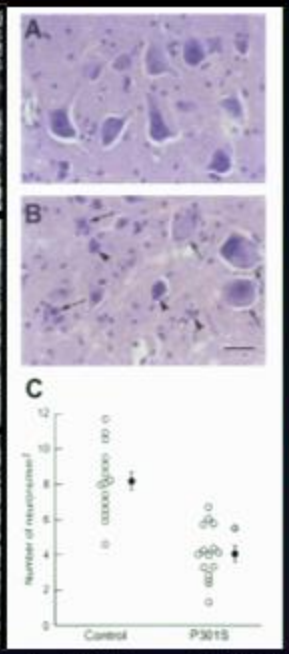
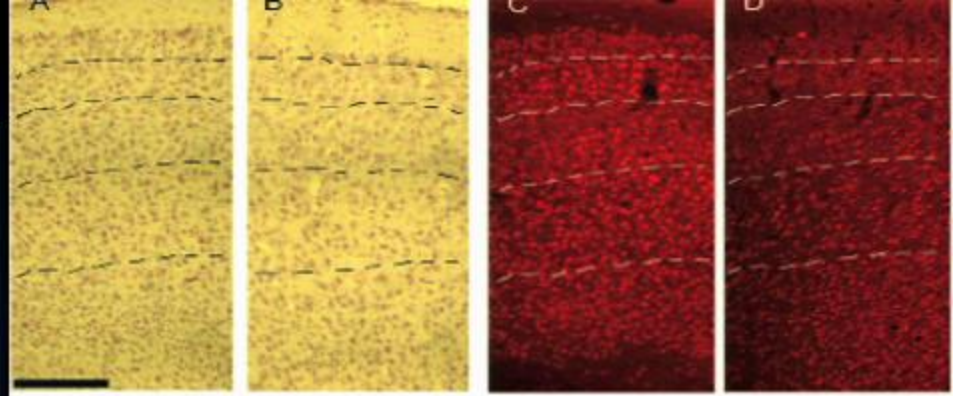
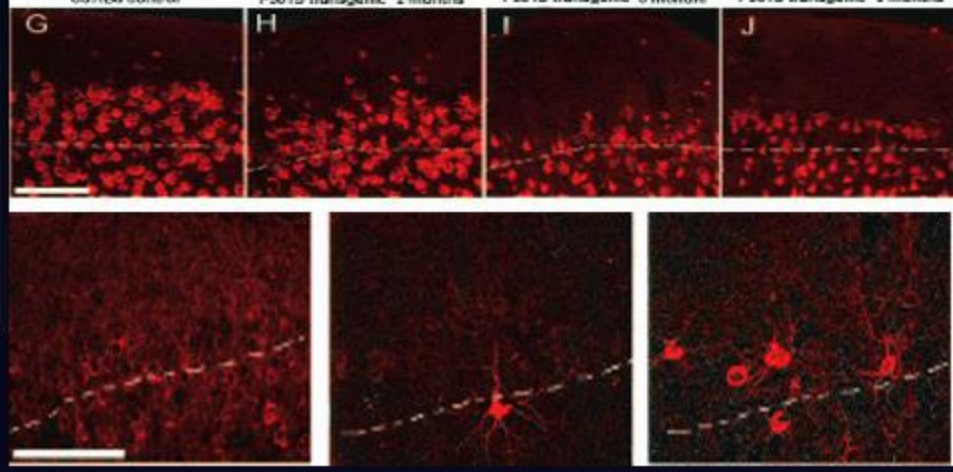


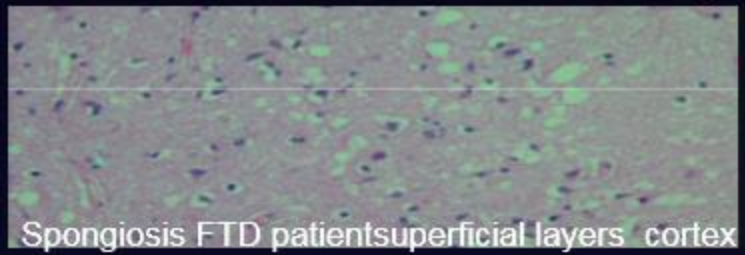




Allen et al. J Neurosci 2002; Hampton et al. J Neurosci 2010







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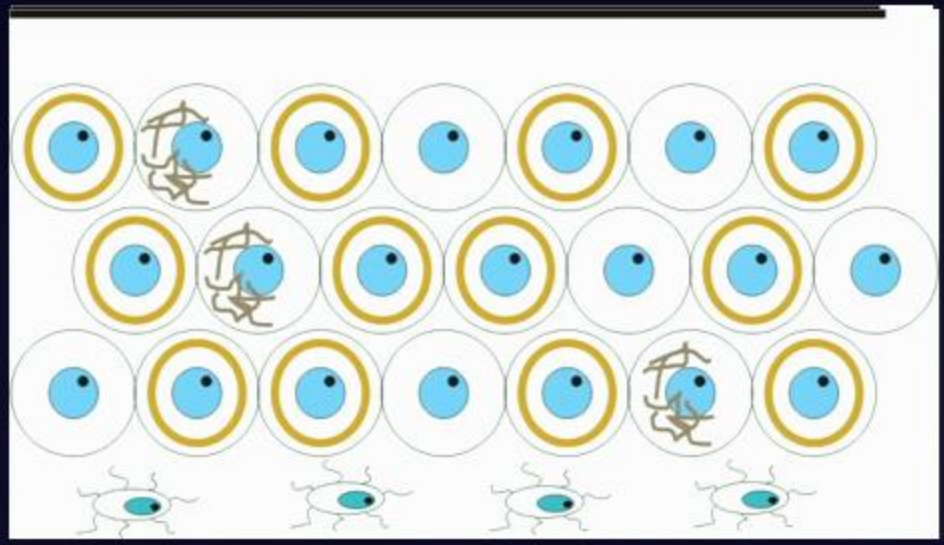
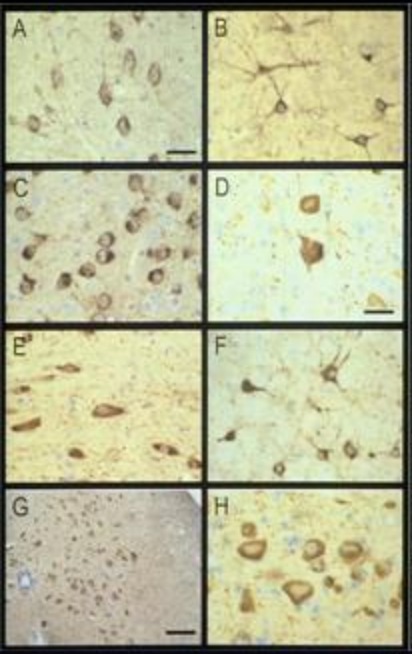
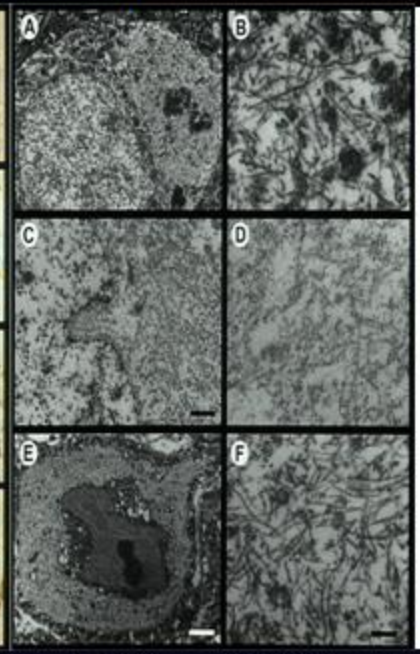
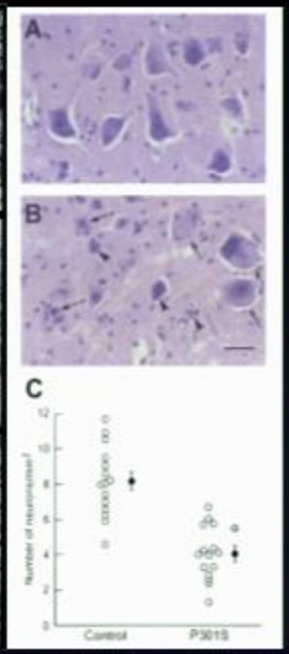


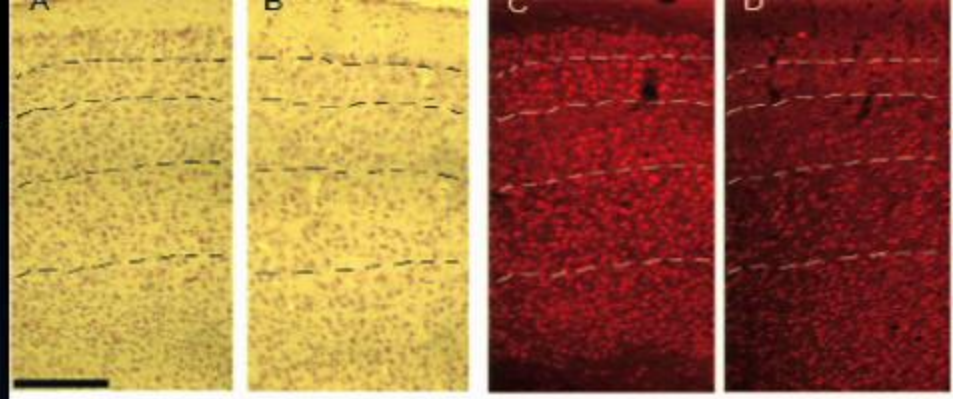
mThy1.2 promoter | P301S *tau* cDNA

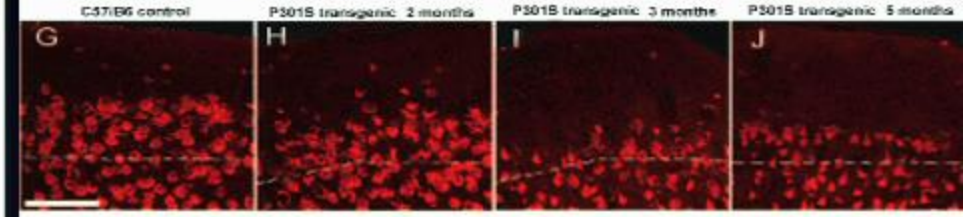


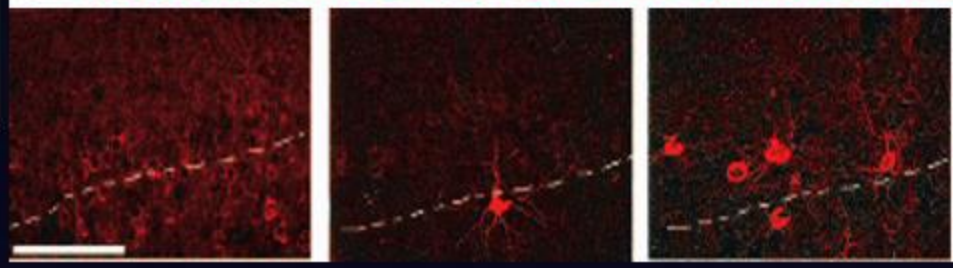


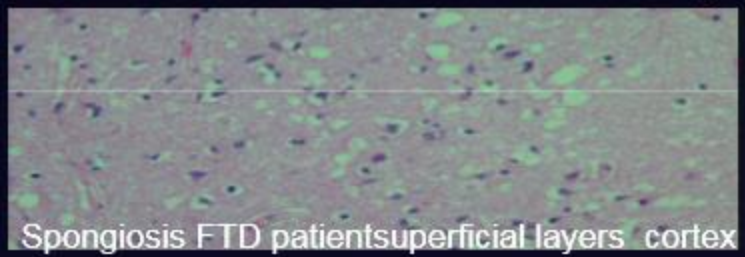


Allen et al. J Neurosci 2002; Hampton et al. J Neurosci 2010





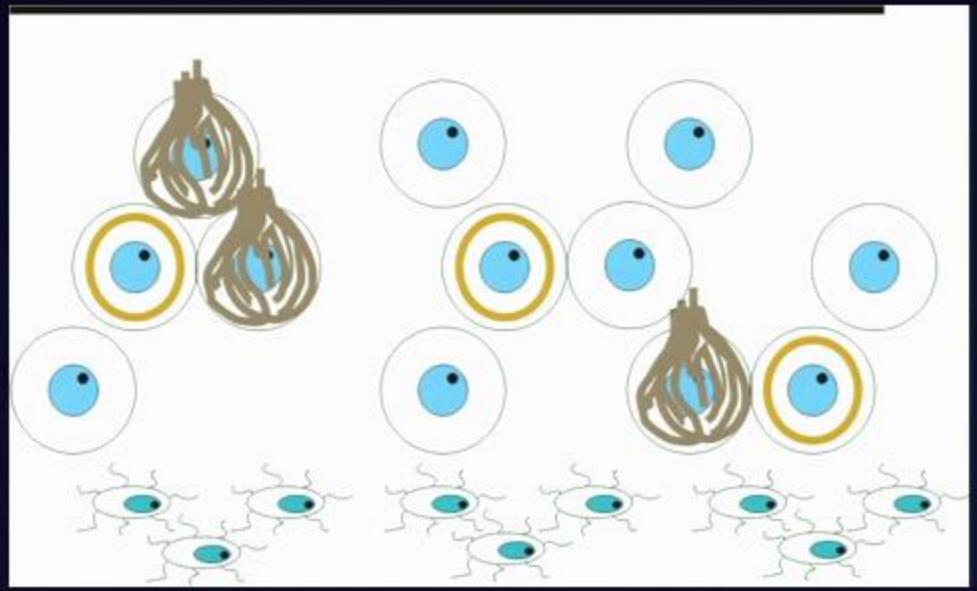




Spongiosis FTD patientsuperficial layers cortex

In P301S tau transgenic mice tau deposits and filaments are present at 5 w and their amount increases up to 4-5 months causing a progressive motor phenotype for which the mice have to be culled at the age of 5-6 months.

FTDP Tau patient cortex



Acta Neuropathol (Berl) (1987) 75:156–159

Acta Neuropathologica
© Springer-Verlag 1987

Neurofibrillary tangles in human upper cervical ganglia

Morphological study with immunohistochemistry and electron microscopy

H. Kawasaki[1], S. Murayama[2], M. Tomonaga[2], N. Izumiyama[3], and H. Shimada[1]

Acta Neuropathol (1993) 85: 453 – 457

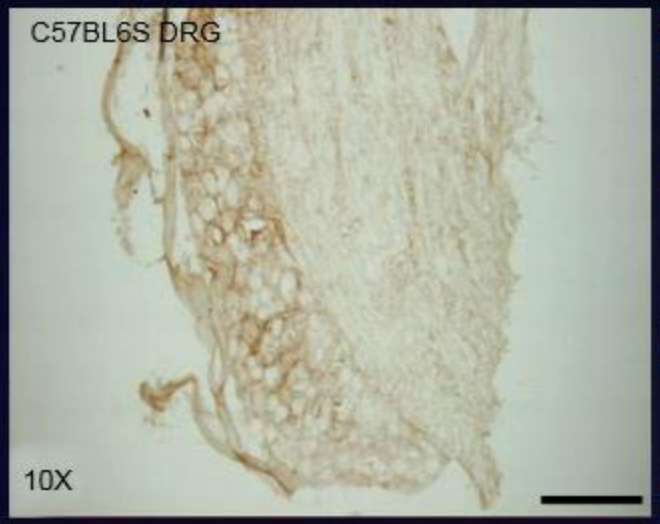
Acta Neuropathologica
© Springer-Verlag 1993

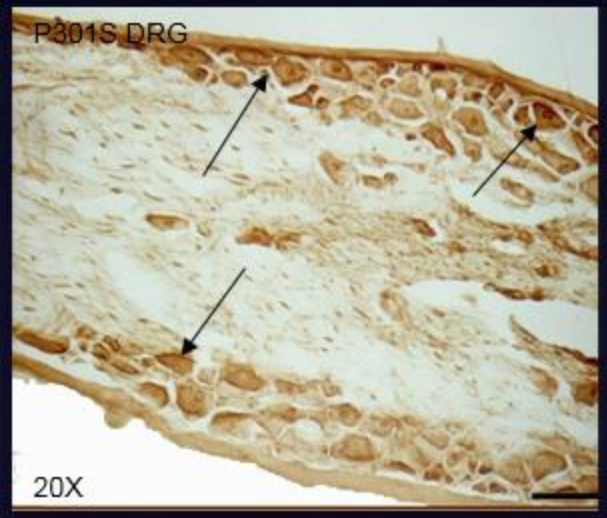
Regular papers

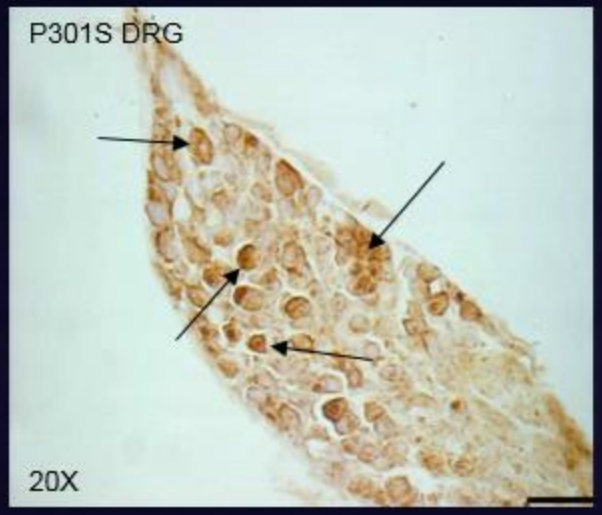
Neurofibrillary tangles in the neurons of spinal dorsal root ganglia of patients with progressive supranuclear palsy*

M. Nishimura[1,2], Y. Namba[2,3], K. Ikeda[4], I. Akiguchi[1], and M. Oda[2]

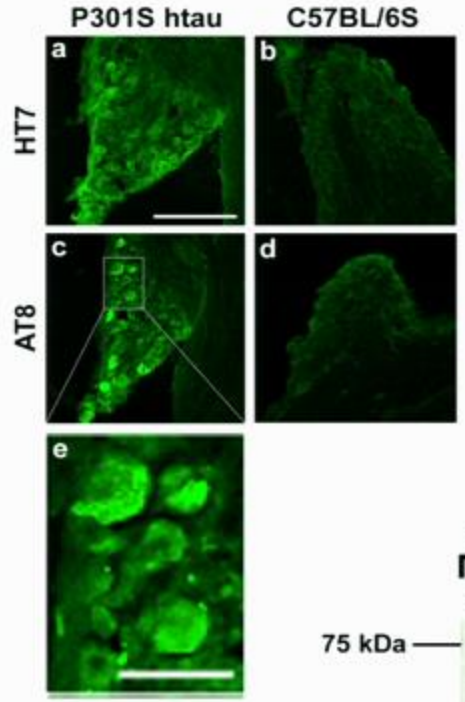
TRANSGENIC TAU HYPERPHOSPHORYLATION IN 5-MONTH-OLD DRG NEURONS OF P301S MICE

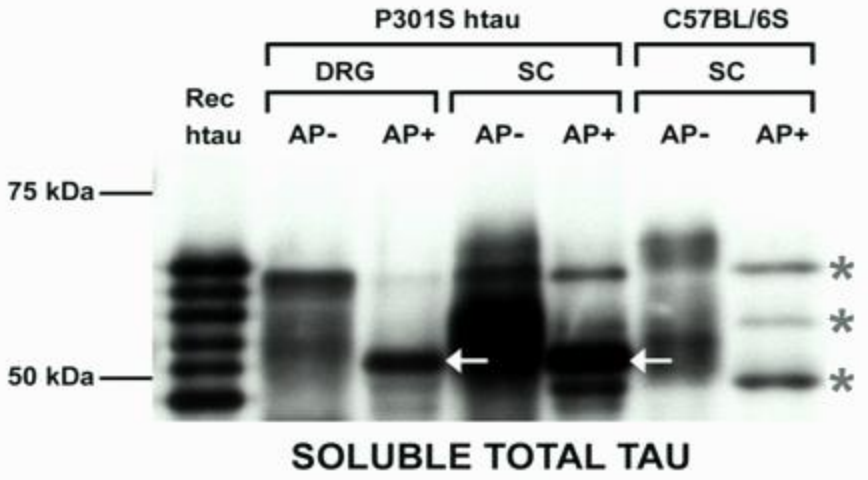




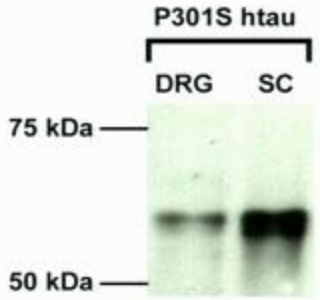


Characterization and effect of P301S tau in DRG

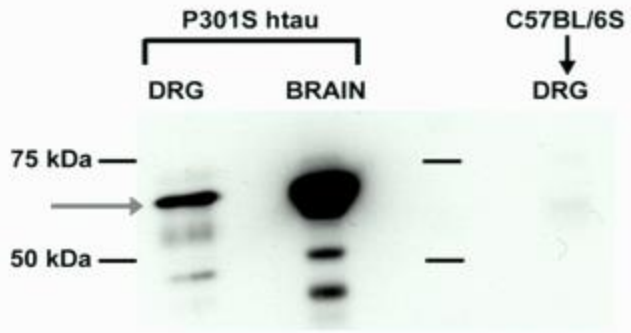




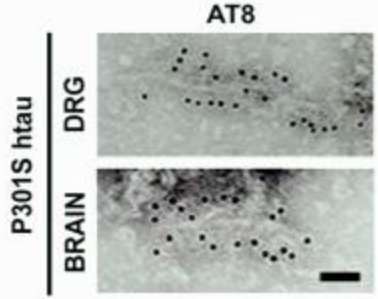
SOLUBLE TOTAL TAU



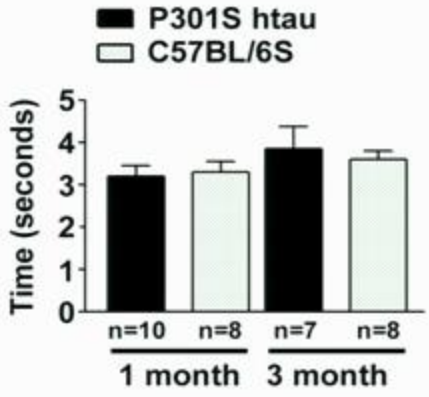
SOLUBLE TAU
AT8



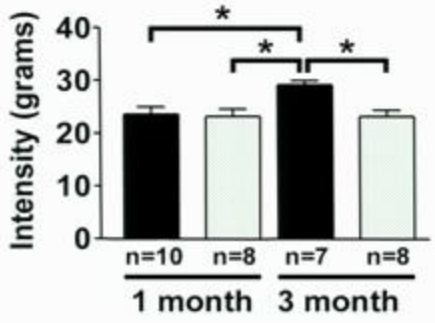
SARKOSYL-INSOLUBLE TAU
AT8



Hot plate test

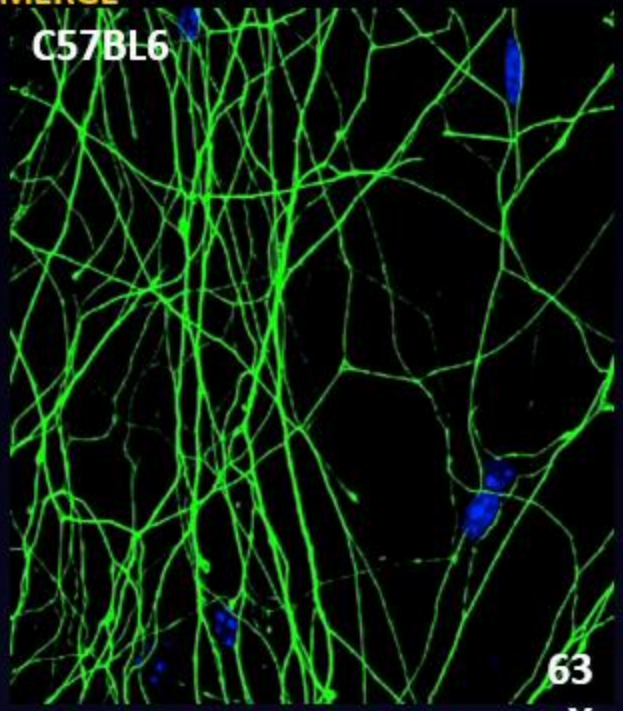


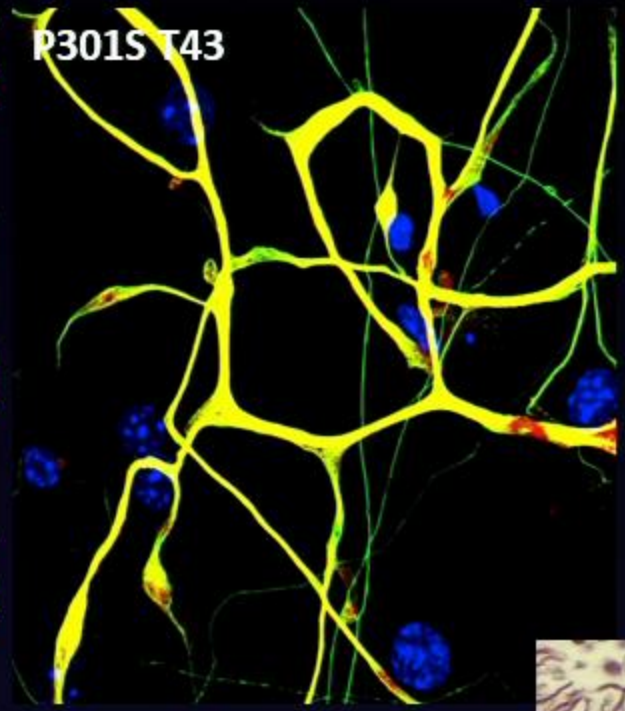
Pressure test

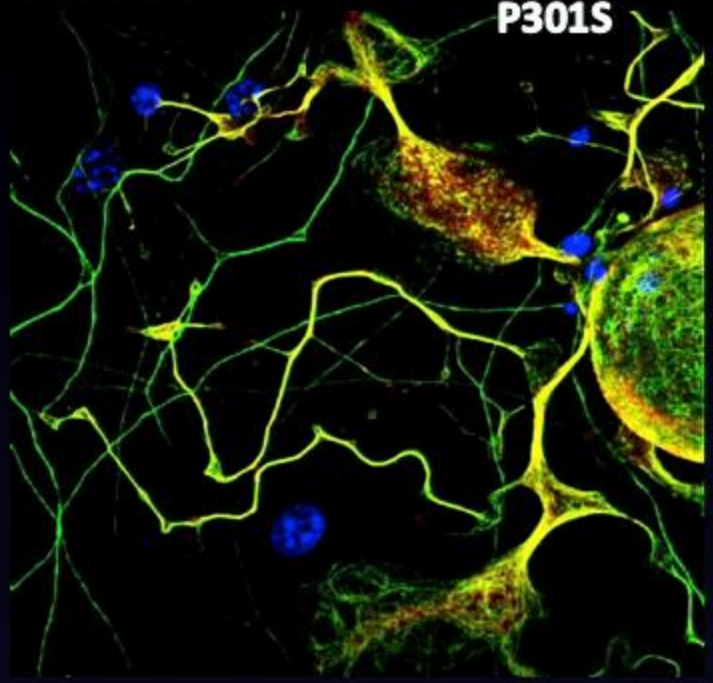


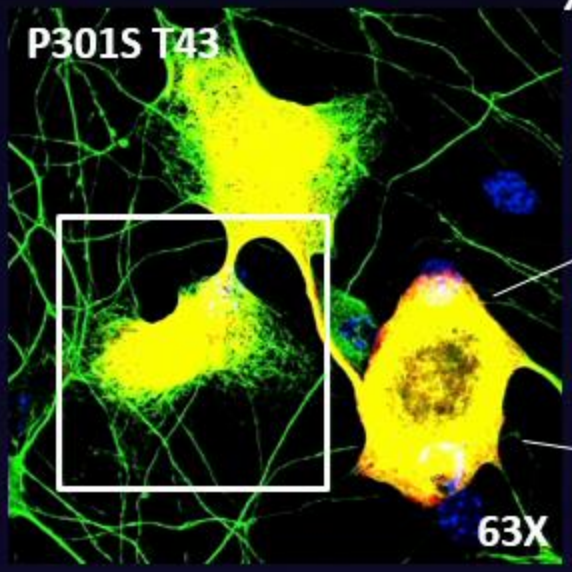
βtubIII
htau
Hoechst33258
MERGE

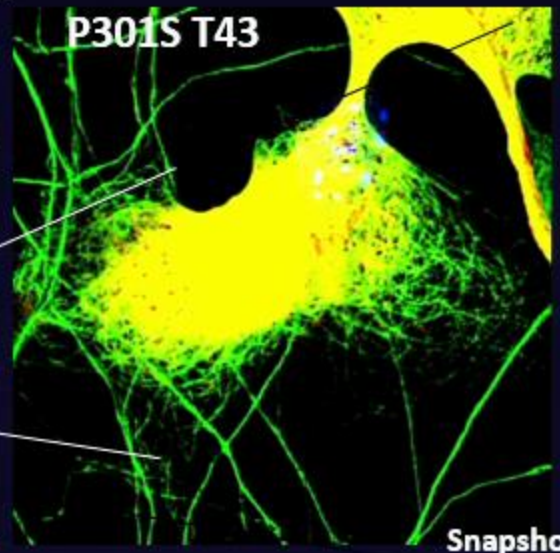
AXONAL PROCESSES AND GROWTH CONES

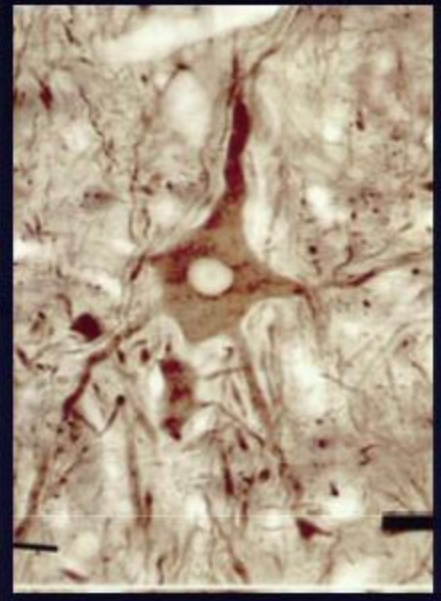






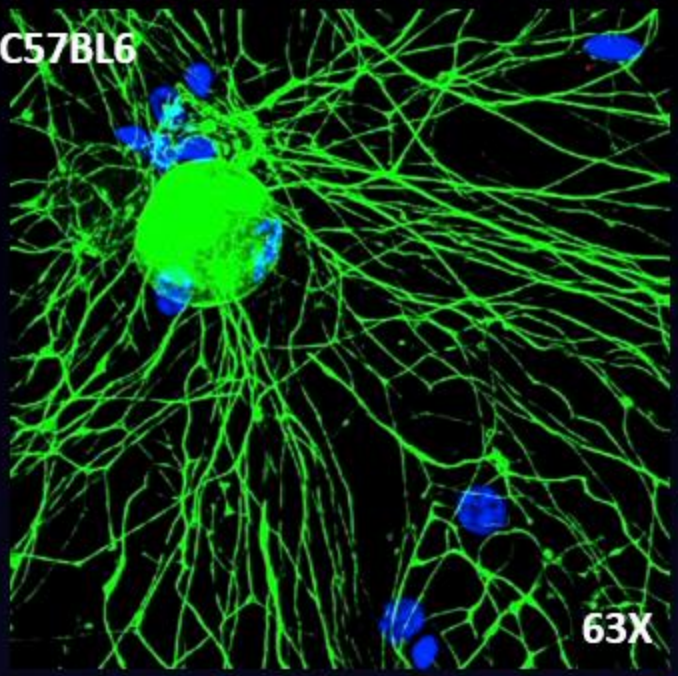


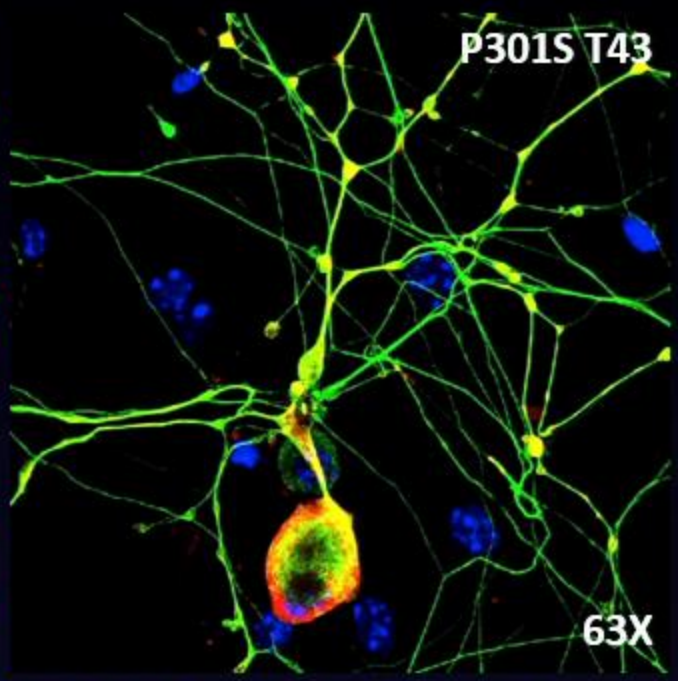




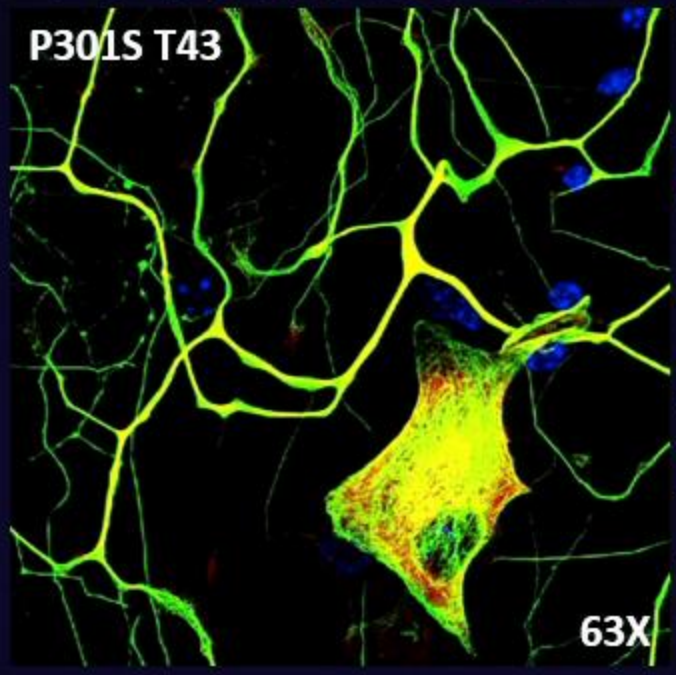
Probst et al. 2000

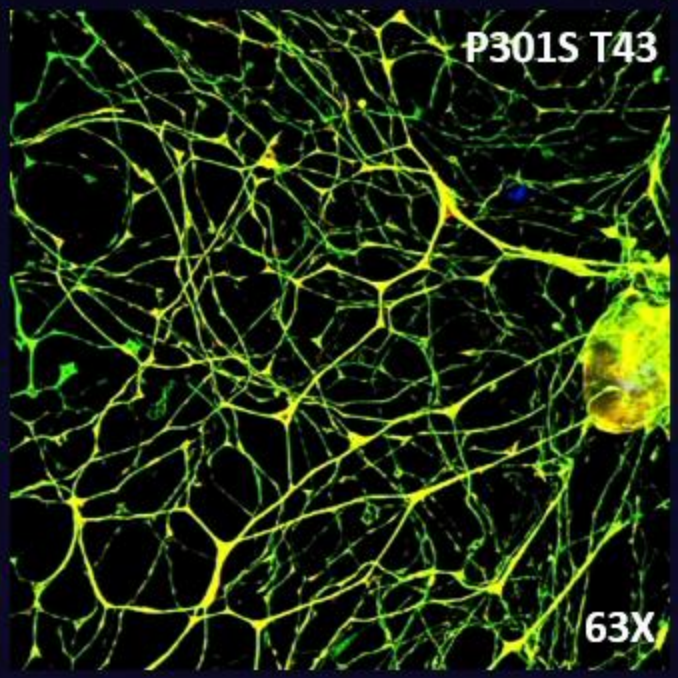
DRG cultures from 5-month-old animals





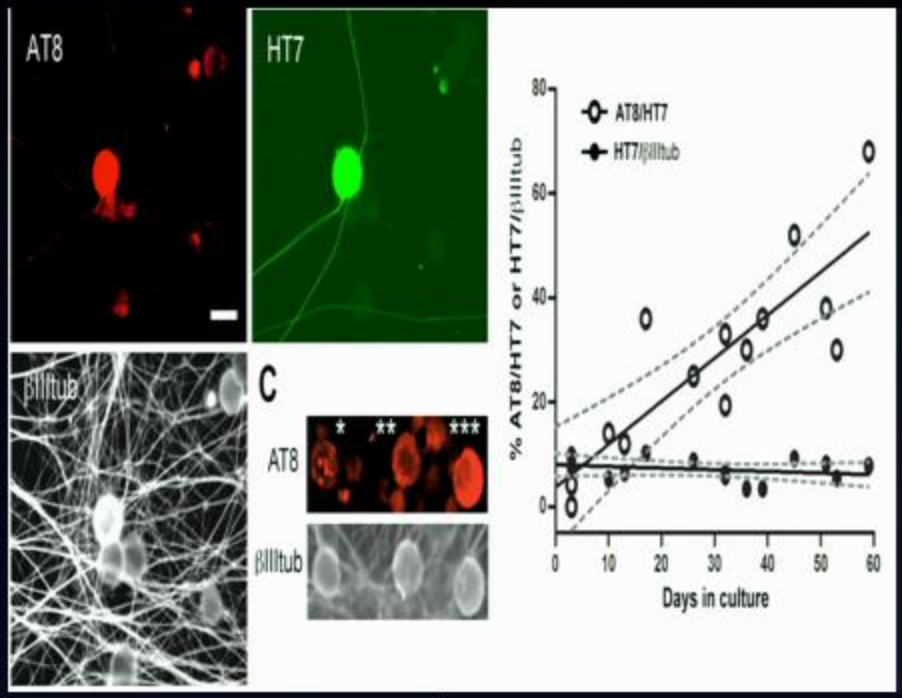
βtubIII
htau
Hoechst33258
MERGE



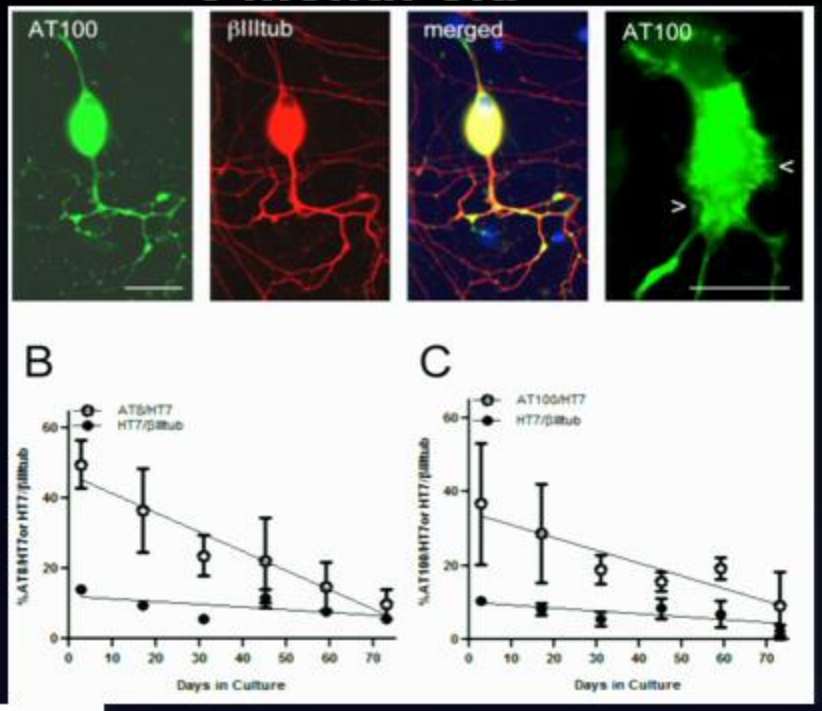


Long term DRG neuronal culture from P301S tau mice

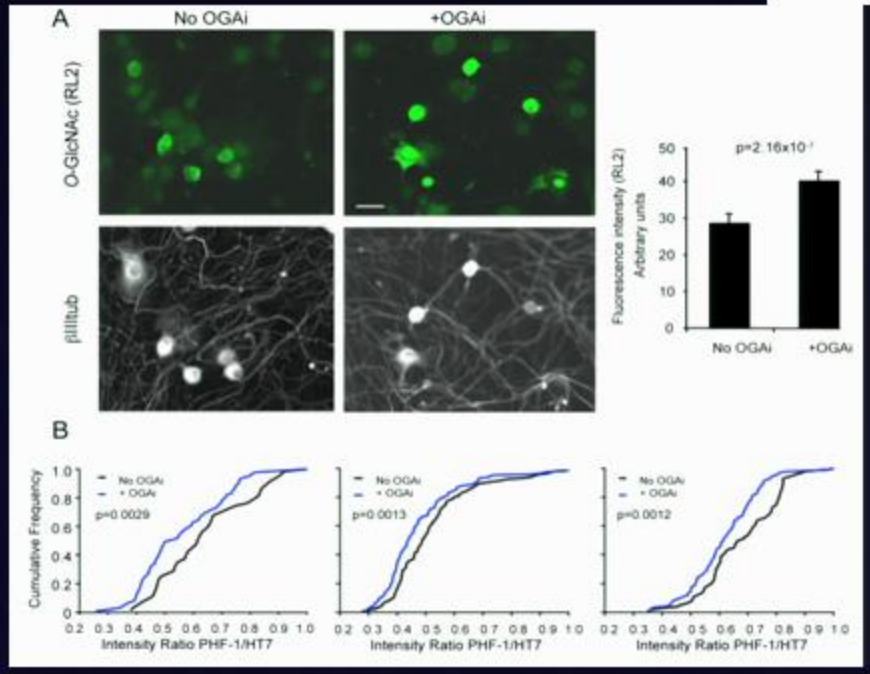
3 month-old



5 month-old

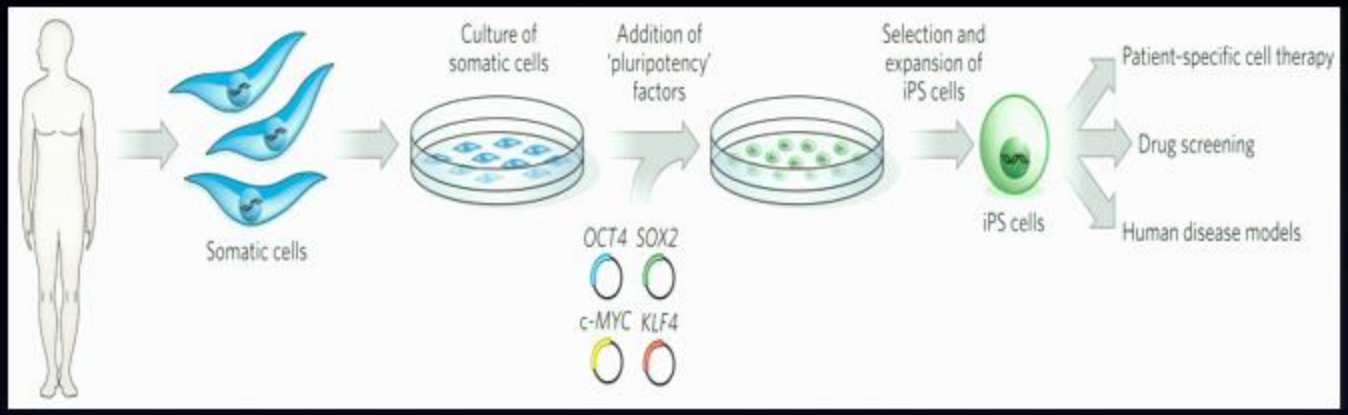


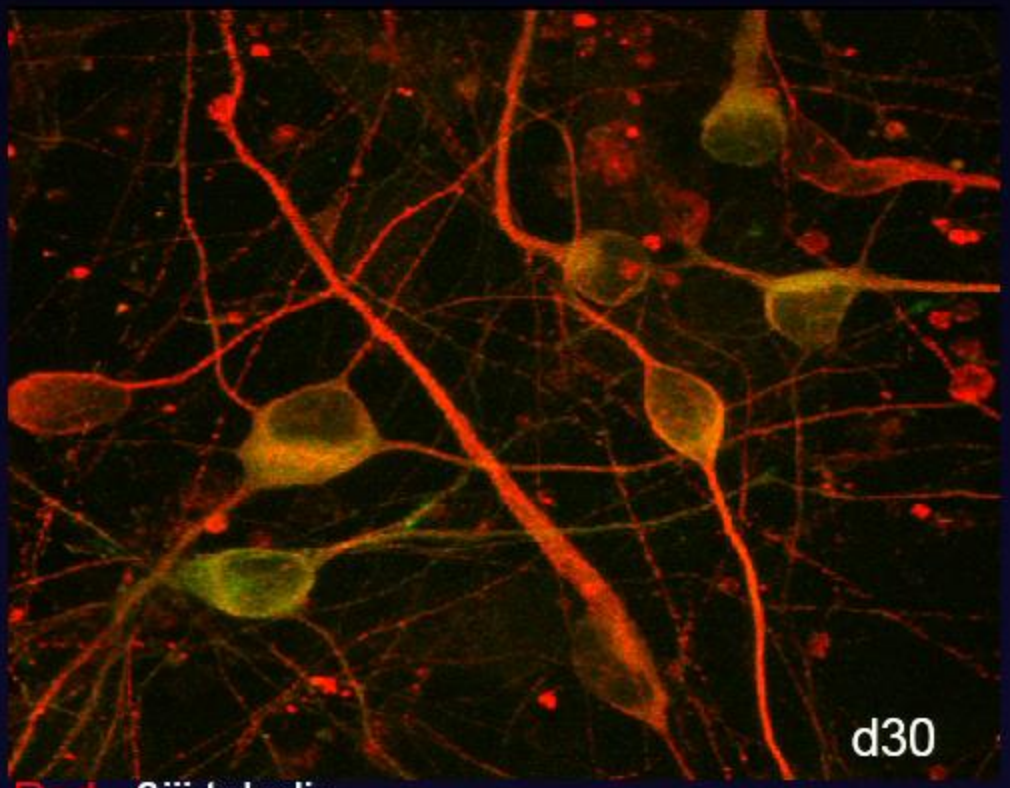
Inhibition of phosphorylation at S396 by O Glucosylation determined in long term DRG cultures

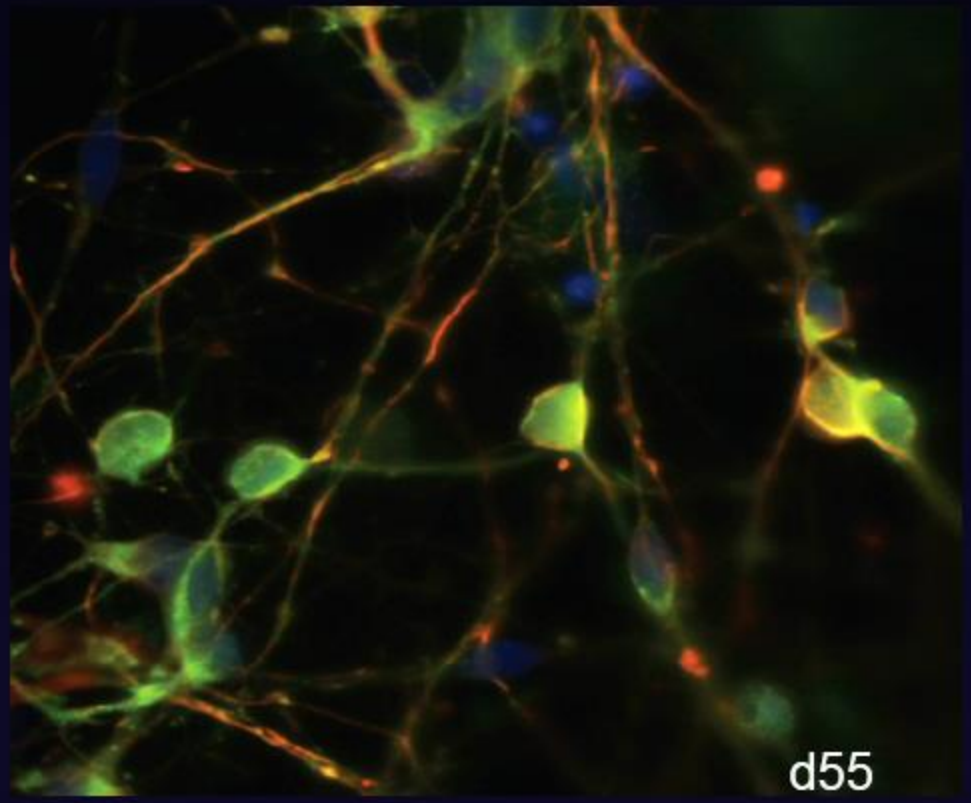


Mellone et al. J Neurosci 2013

Neuroni da Fibroblasti di pazienti con mutazioni nel gene della Tau



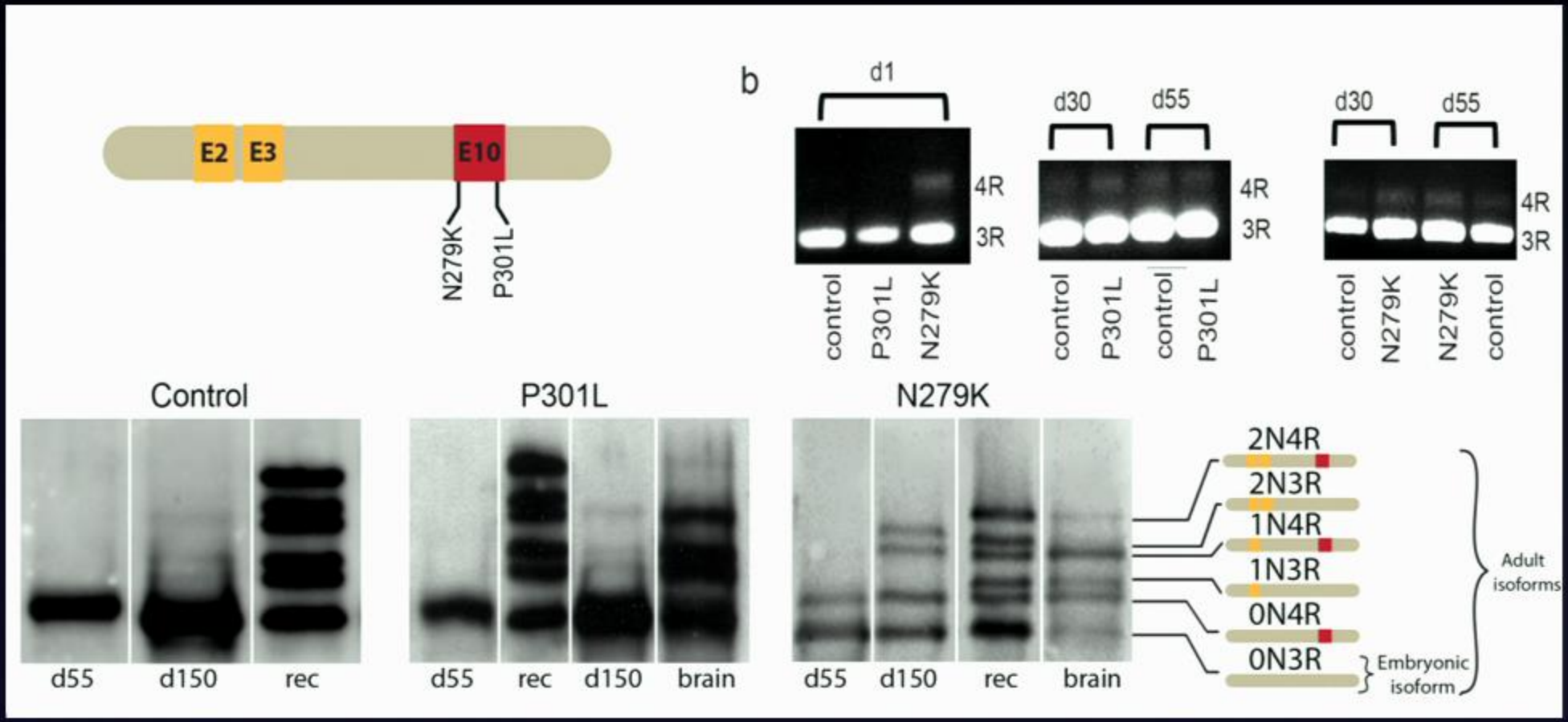




Red= ßiii tubulin,
Green= Tau

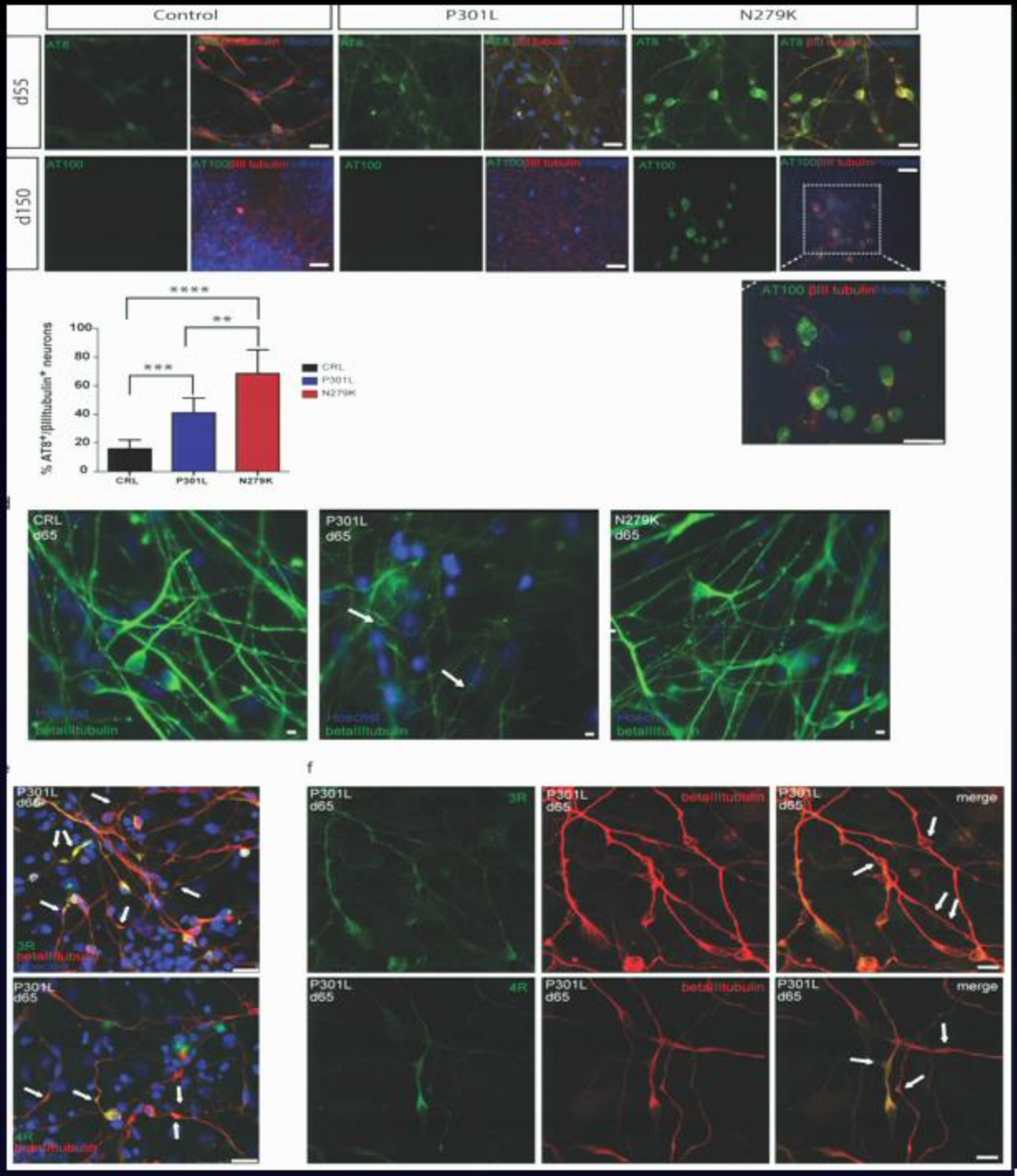
Iovino et al. unpublished

Time course of tau isoform expression in IPSC-derived neurones from control, P301L and N279K patients



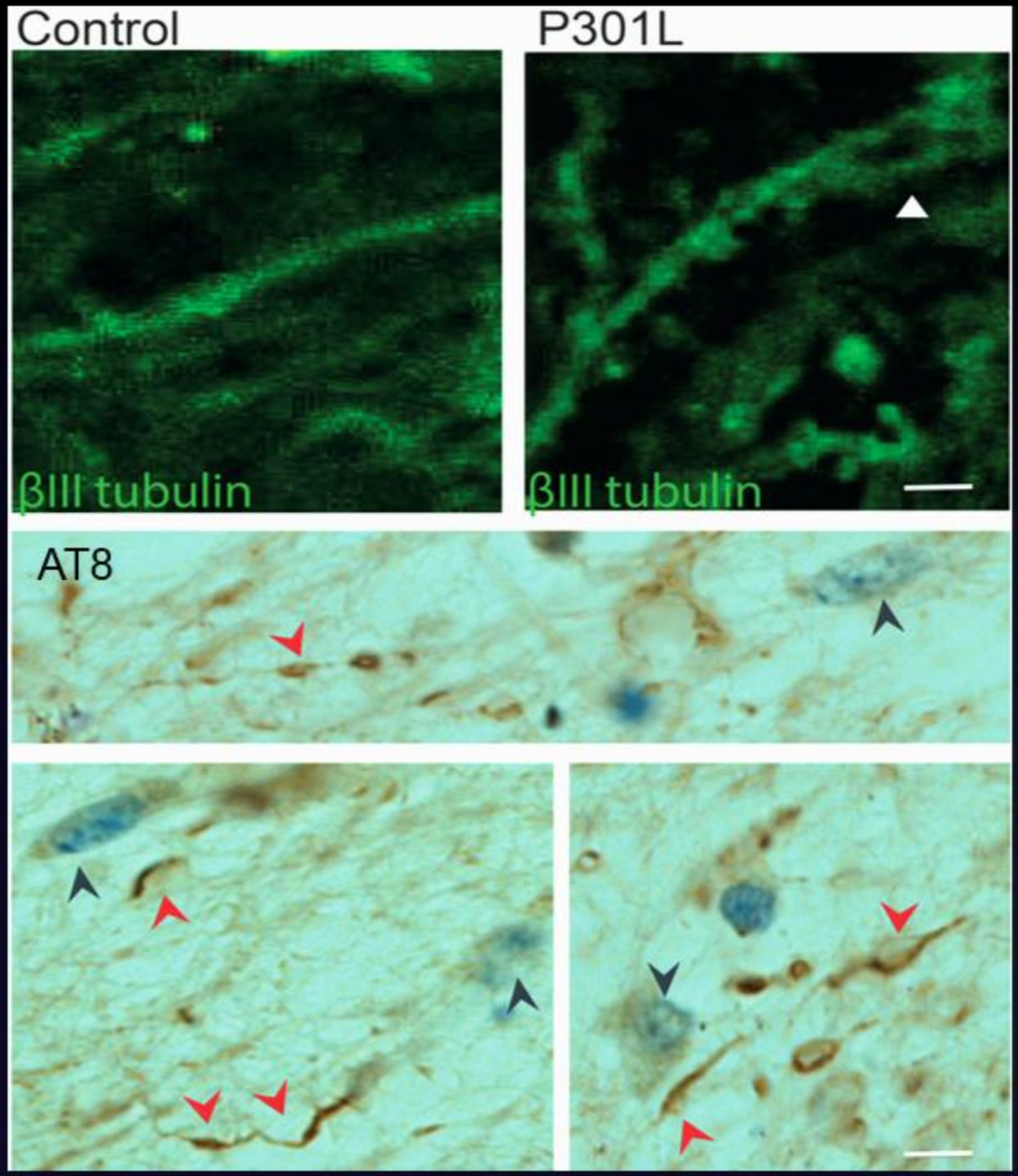
Iovino et al. unpublished

Tau phosphorylation and morphology in IPSC-derived neurones



lovino et al. unpublished

Varicosity-like structures in the brains of P301L tau patients



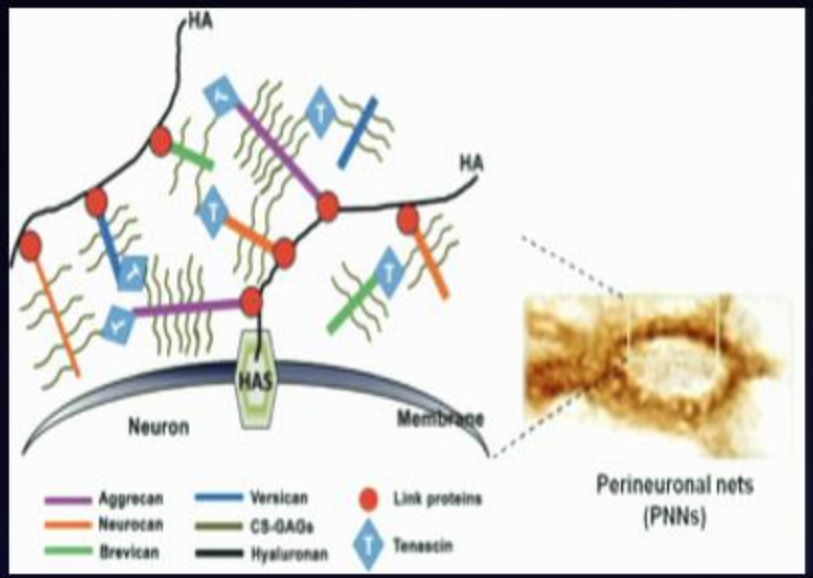
Iovino et al. unpublished

Puo' l'aumento di plasticita' migliorare I sintomi in malattie con aggregati di tau? **Per sapere questo avevamo bisogno di:**

1-identificare un'area specifica del cervello a cui potesse essere riferito un comportamento specifico

2- identificare un metodo per aumentare la plasticita';

Perineuronal net (PNN) e' una struttura molto organizzata della matrice extracellulare che si sviluppa dopo la nascita e inibisce la rigenerazione e plasticita' nel SNC.

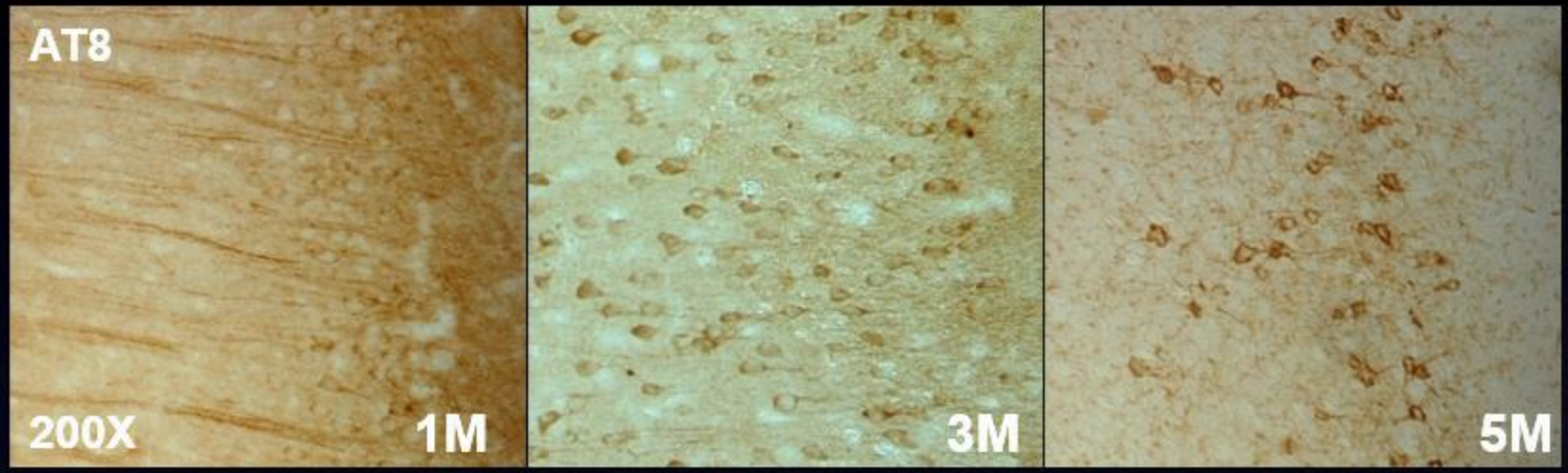


Per aumentare la plasticita' si puo' rimuovere il PNN on Chondroitinase ABC or link protein e questo ha dimostrato un aomento della memoria correlata con il riconoscimento di oggetti (OR). memory

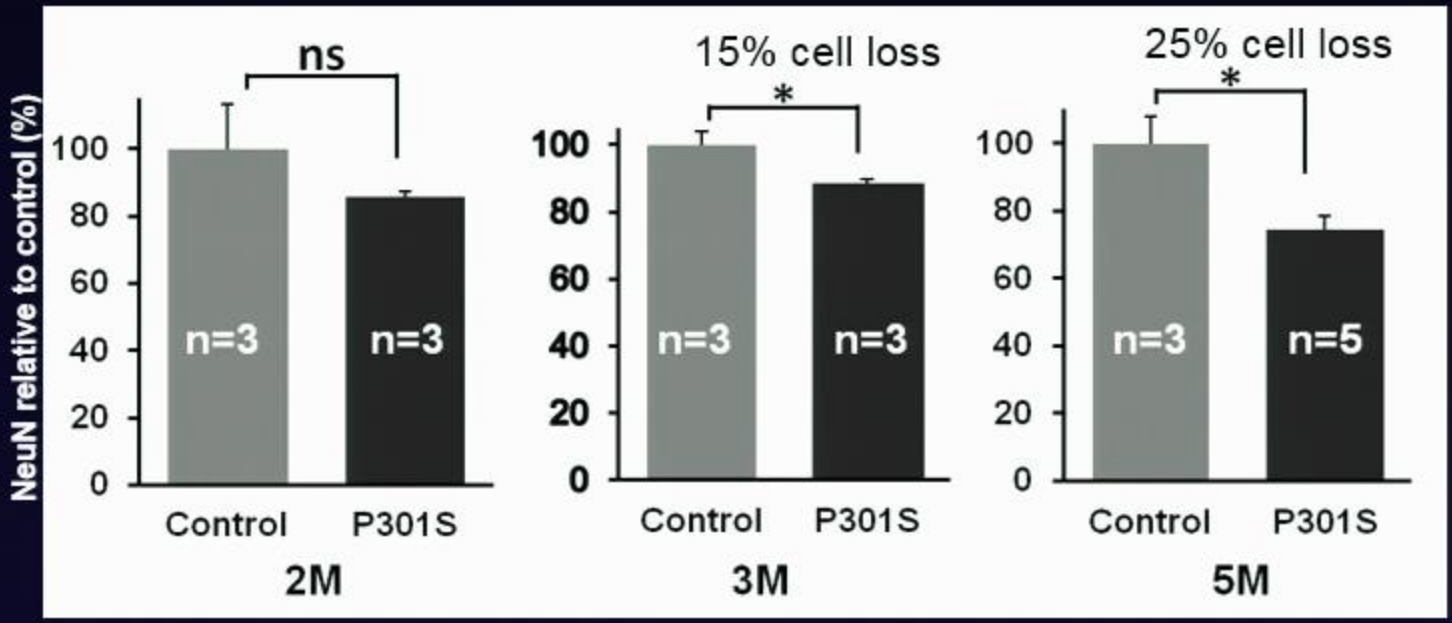
1-Perirhinal cortex e' coinvolta nella memoria correlata con il riconoscimento di oggetti;

2-La chondroitinase puo' essere utilizzata per rimuovere il PNN;

Progressive tau pathology in the Perirhinal cortex of P301S mice

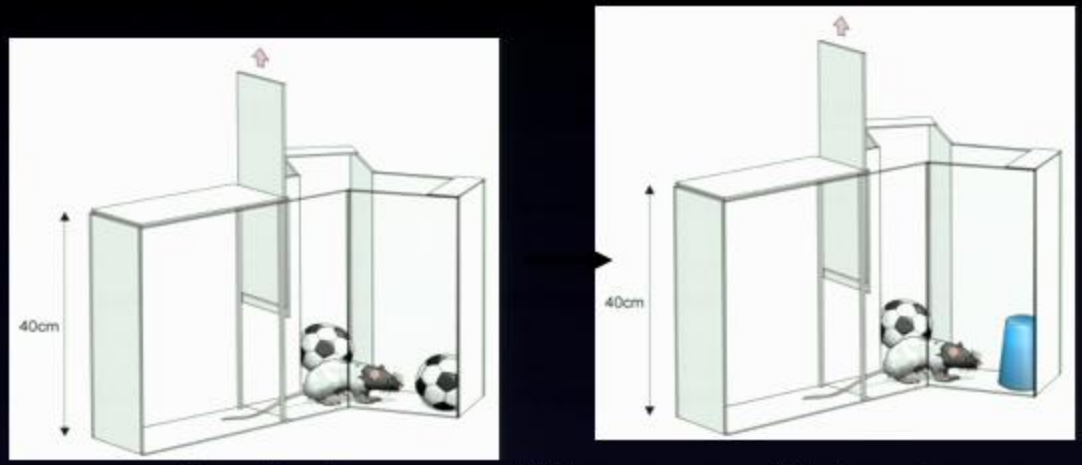


Progressive cell loss



Yang S et al. 2014

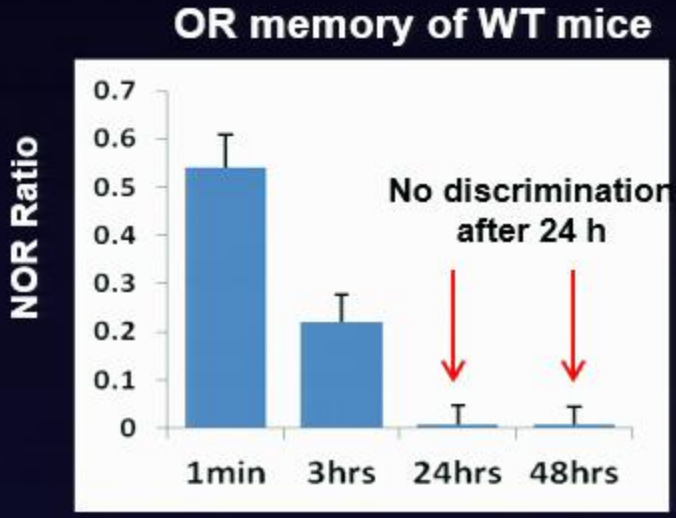
Novel object recognition (NOR) test



Sample phase (5 min) | Delay (1 min or 3 hr) | Choice phase (5 min)

Object pairs for NOR test

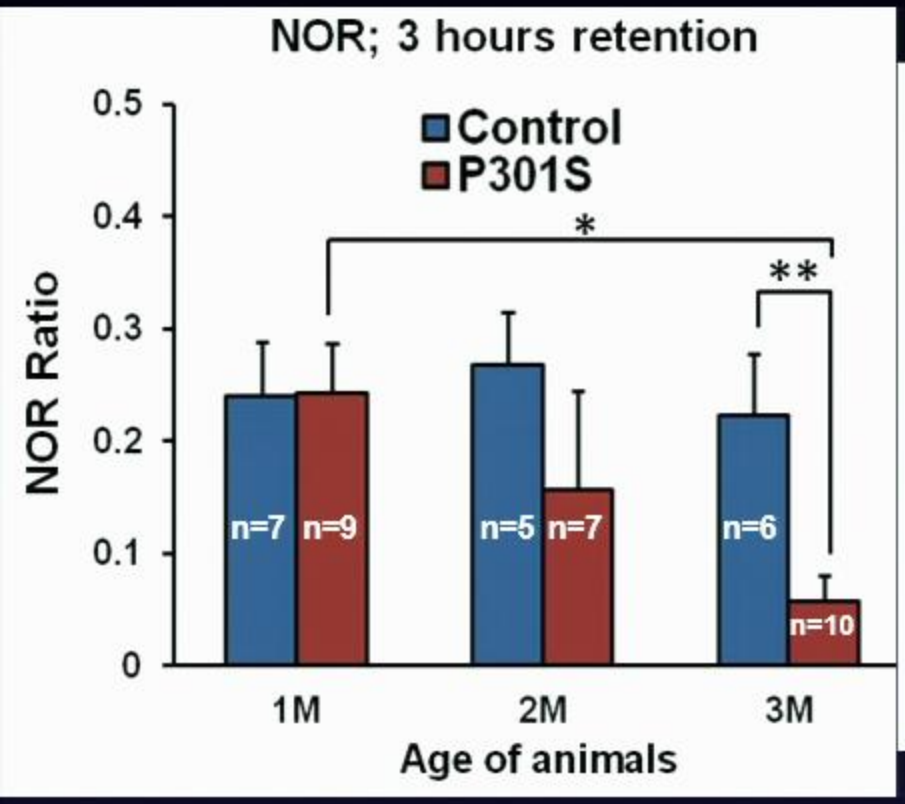
Analysis: NOR ratio=(novel - familiar object exploration) / total choice exploration

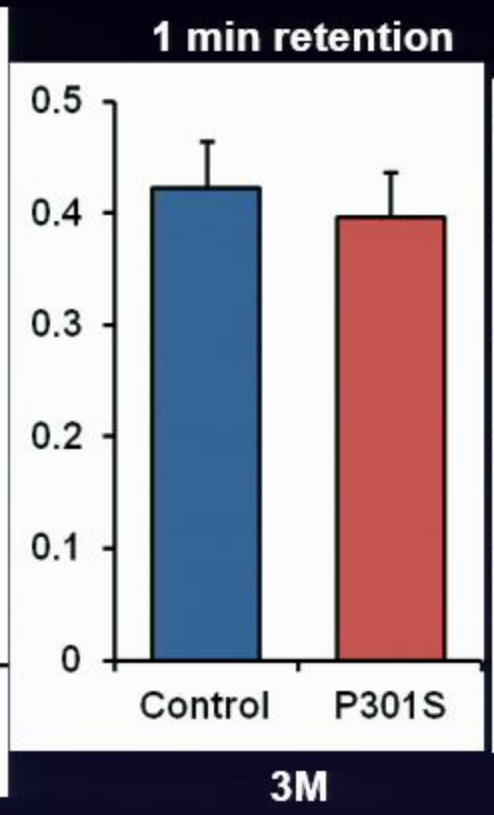


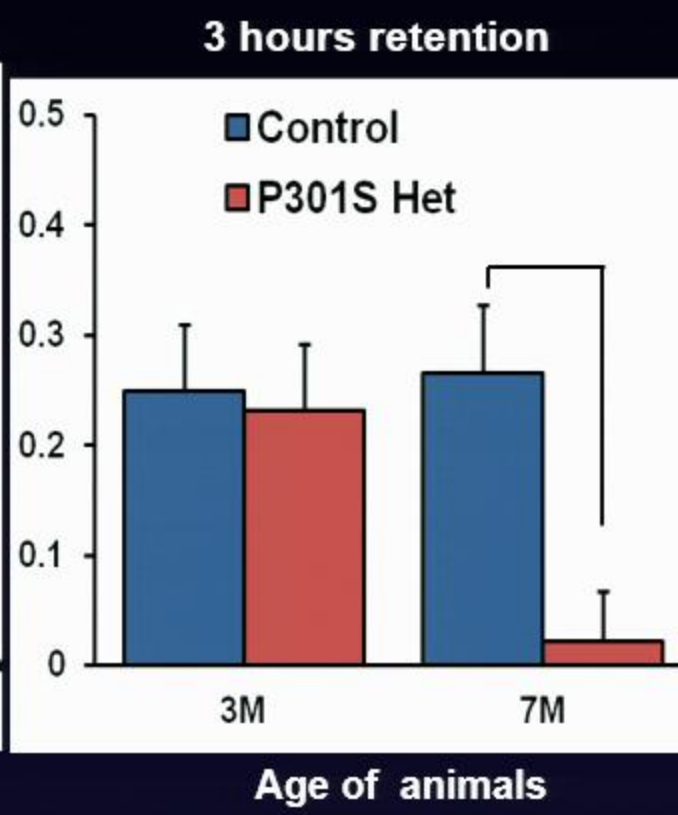
- NOR task using Y maze is the perirhinal (PRh) cortex dependent and lesion of the PRh cortex abolishes OR memory

(Mumby DG *et.al*, 1994; Bartko SJ *et.al*, 2007; B.D. Winters *et.al*, 2010; Stephanie M. McTighe, *et al.* Science)

Temporal progression of OR memory deficit in Tg P301S mice







Homozygous mice

heterozygous mice

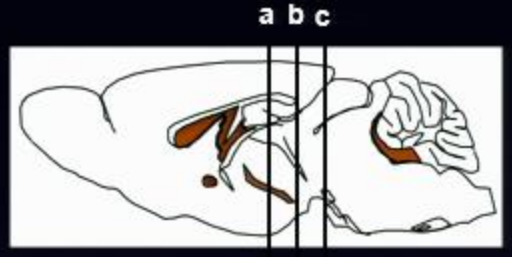
Yang S et al. 2014

ChABC treatment enhanced OR memory in Tg P301S mice

A

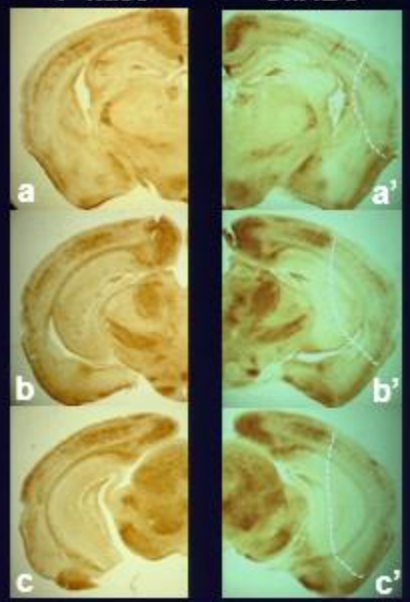
0.5 µl/injection/6 sites in total

50U/ml conc.



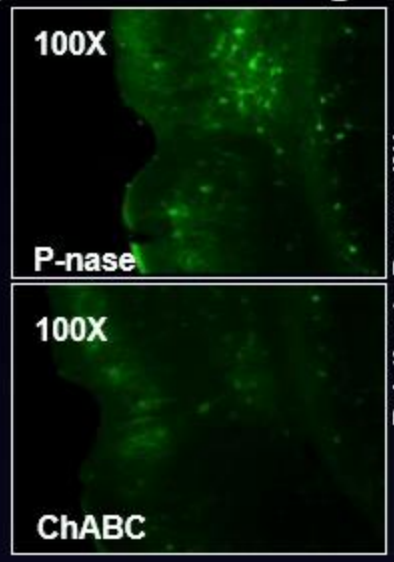
a: bregma -1.82mm
b: bregma -2.80mm
c: bregma -3.80mm

Modified from brain atlas

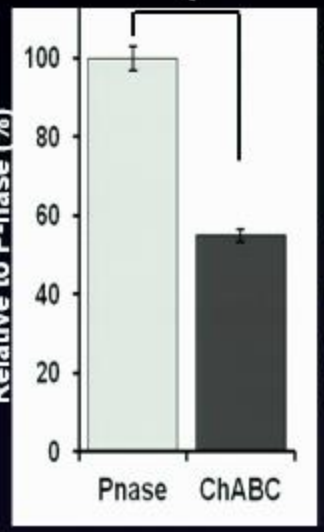


WFA staining

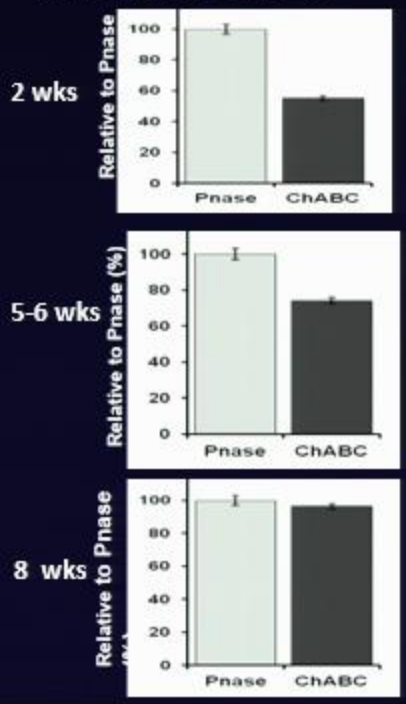
B WFA staining



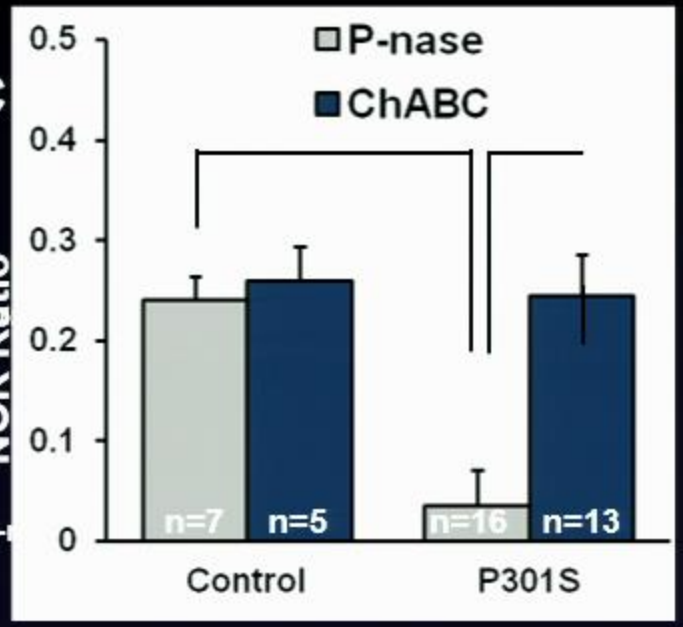
Reduction of PNNs



Time-dependent amount of PNNs after ChABC

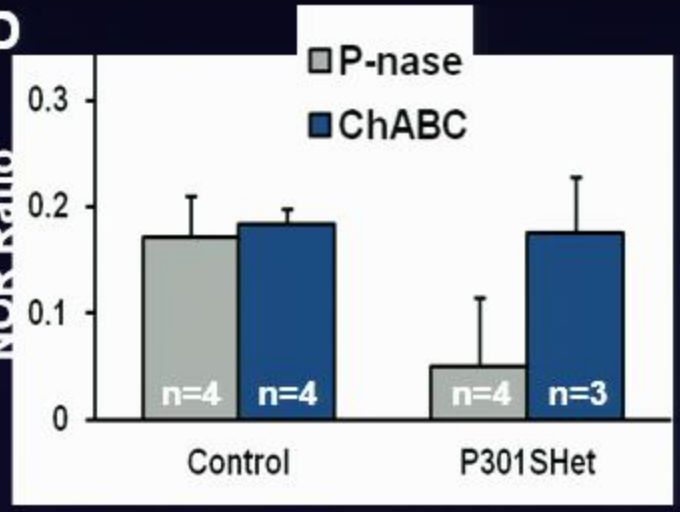


C



3 months homozygous mice

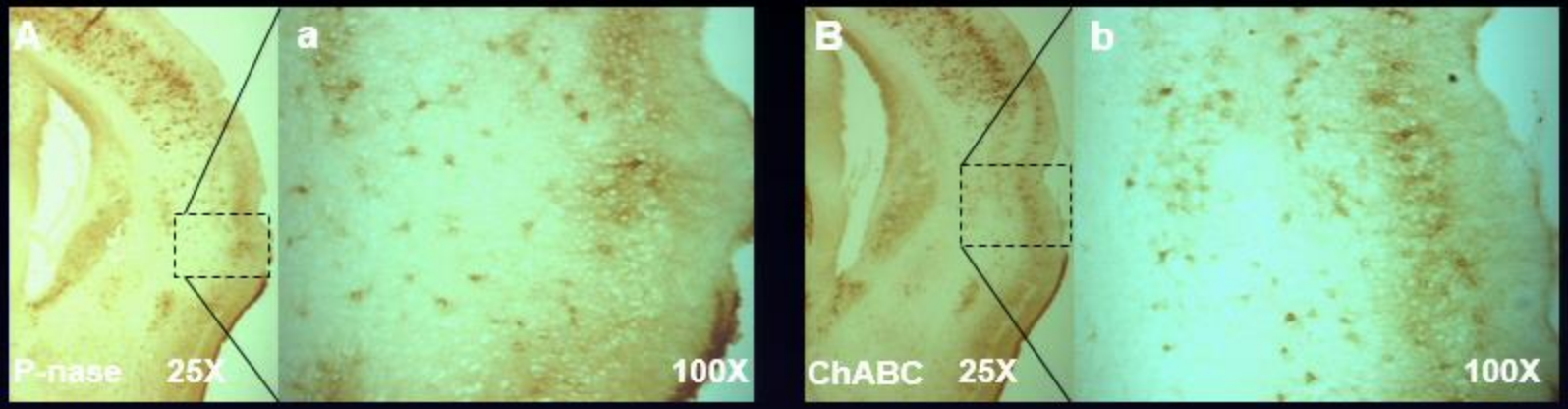
D



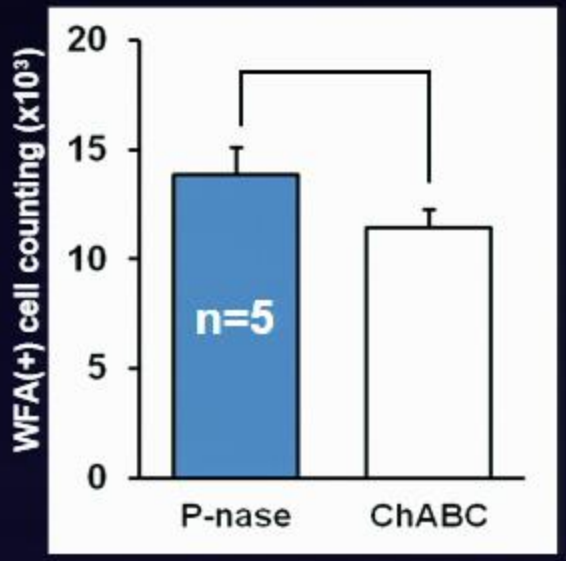
7 months heterozygous mice

Yang S et al. 2014

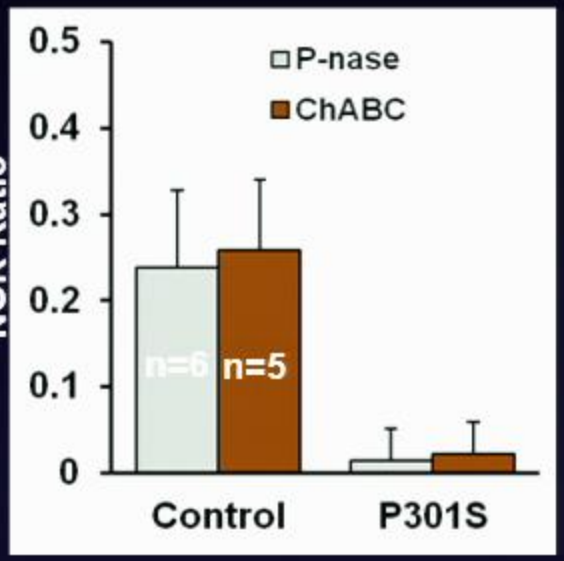
OR memory deficit returns 5 weeks after ChABC treatment in Tg P301S mice



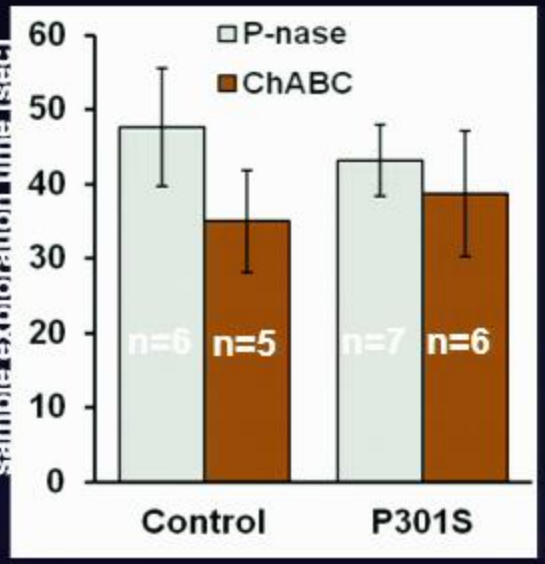
C Number of PNN (+) cells



D 3 hours retention



E Level of motivation



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Conclusions

L’aumento di plasticita’ puo’ migliora la memoria, anche se in modo temporaneo, nei soggetti con patologia tau

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