MRC Laboratory of Molecular Biology

Understanding Neurodegenerative Diseases

Michel Goedert


SIGNAL CORPS


CHELSEA REMEMBERS
PRIDE OF LONDO

FC HAUTCHARAGE

COUPE D'EUROPE DES VAINQUEURS DE COUPES - FINALES

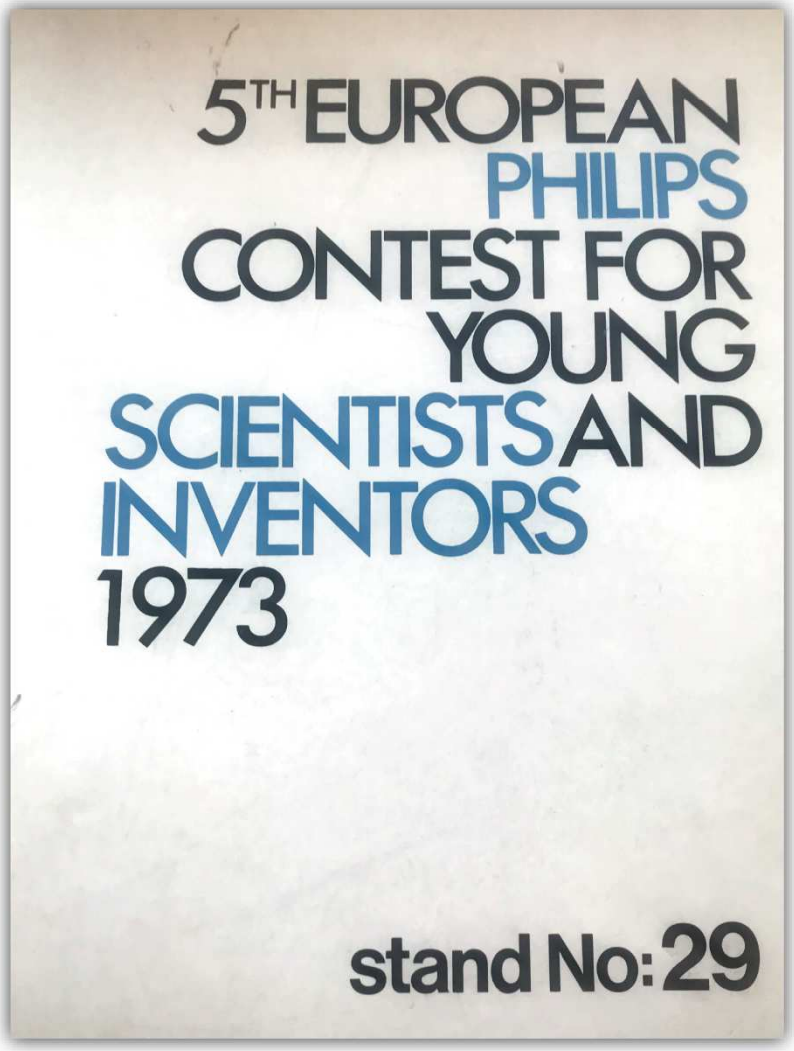
1/16e

CHELSEA LONDON

Luxembourg

Luxembourg

Luxembourg


5TH EUROPEAN
PHILIPS
CONTEST FOR
YOUNG
SCIENTISTS AND
INVENTORS
1973
stand No: 29

Luxembourg

Basel

Basel

Herbsttag

Herr: es ist Zeit. Der Sommer war sehr groß.
Leg deinen Schatten auf die Sonnenuhren,
und auf den Fluren laß die Winde los.

Befiel den letzten Früchten voll zu sein;
gib ihnen noch zwei südlichere Tage,
dränge sie zur Vollendung hin und jage
die letzte Süße in den schweren Wein.

Wer jetzt kein Haus hat, baut sich keines mehr.
Wer jetzt allein ist, wird es lange bleiben,
wird wachen, lesen, lange Briefe schreiben
und wird in den Alleen hin und her
unruhig wandern, wenn die Blätter treiben.

Rainer Maria Rilke

Basel

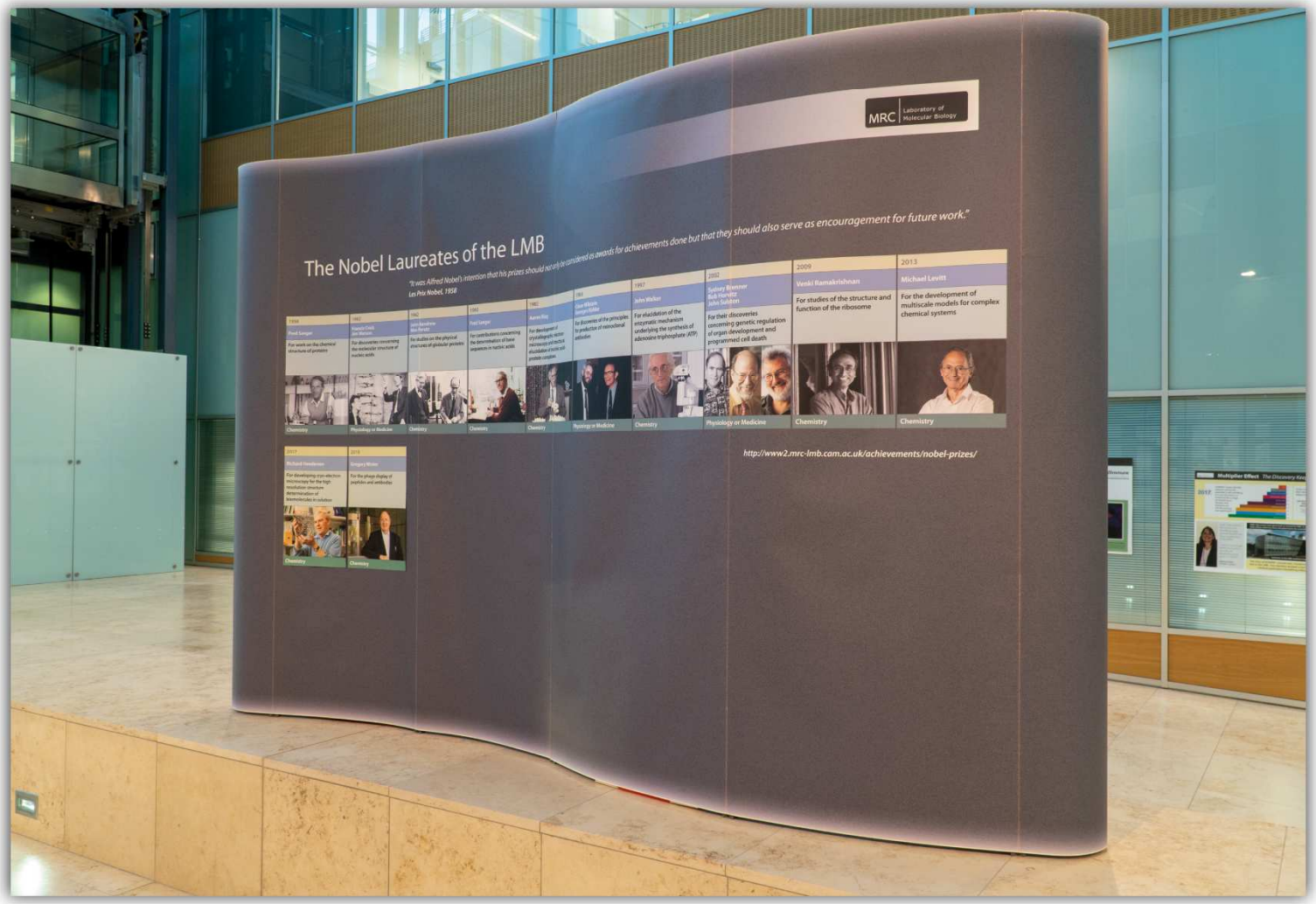
Basel

Cambridge

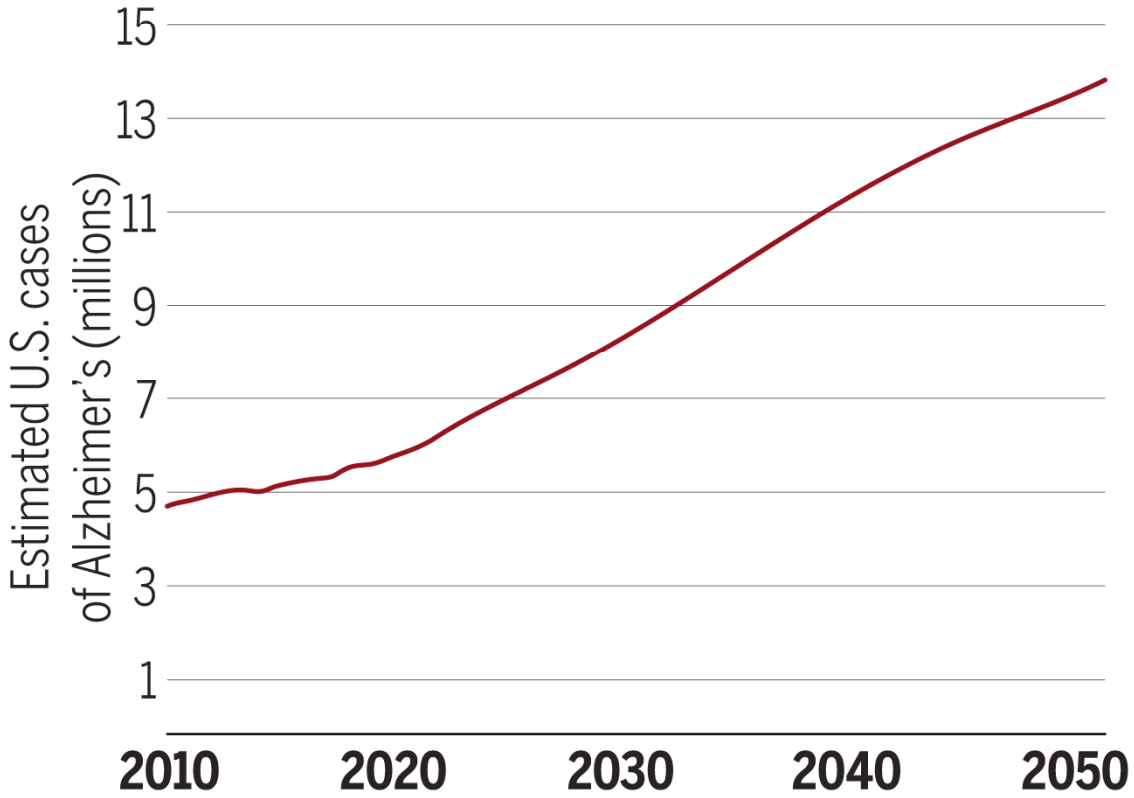
Cambridge

Cambridge

Cambridge


MRC Laboratory of Molecular Biology
The Nobel Laureates of the LMB
"It was Alfred Nobel's intention that his prizes should not only be considered as awards for achievements done but that they should also serve as encouragement for future work."
Les Prix Nobel, 1958
1958
Fred Sanger
For work on the chemical structure of proteins
Chemistry
1962
Francis Crick
John Kendrew
Max Perutz
For discoveries concerning the molecular structure of nucleic acids
Physiology or Medicine
1962
John Kendrew
Max Perutz
For studies on the physical structures of globular proteins
Chemistry
1980
Fred Sanger
For contributions concerning the determination of base sequences in nucleic acids
Chemistry
1982
Aaron Klug
For development of crystallographic electron microscopy and structural elucidation of nucleic acid-protein complex
Chemistry
1984
Cesar Milstein
Georges Köhler
For discovery of the principles for production of monoclonal antibodies
Physiology or Medicine
1997
John Walker
For elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP)
Chemistry
2002
Sydney Brenner
Bob Horvitz
John Sulston
For their discoveries concerning genetic regulation of organ development and programmed cell death
Physiology or Medicine
2009
Venki Ramakrishnan
For studies of the structure and function of the ribosome
Chemistry
2013
Michael Levitt
For the development of multiscale models for complex chemical systems
Chemistry
2017
Richard Henderson
For developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution
Chemistry
2018
Gregory Winter
For the phage display of peptides and antibodies
Chemistry
http://www2.mrc-lmb.cam.ac.uk/achievements/nobel-prizes/

Alzheimer's disease in the U.S.



Neurodegenerative Diseases

Alzheimer's disease
Parkinson's disease
Dementia with Lewy bodies
Frontotemporal dementias (including Pick's disease)
Progressive supranuclear palsy
Corticobasal degeneration
Chronic traumatic encephalopathy
Argyrophilic grain disease
Tangle-only dementia
Multiple system atrophy
Huntington's disease
Motor neuron diseases
Prion diseases

Protein assemblies in nerve cells and/or glial cells

No mechanism-based therapies

Common Features

- Neurodegenerative diseases are age-dependent.
- Protein assembly begins in a specific region of the brain for a given neurodegenerative disease, from where it appears to spread to other areas.
- Most disease cases are sporadic, but others are inherited, often in an autosomal-dominant manner (Huntington's disease is always inherited).
- Close links exist between protein assembly and the causes of inherited forms of disease.

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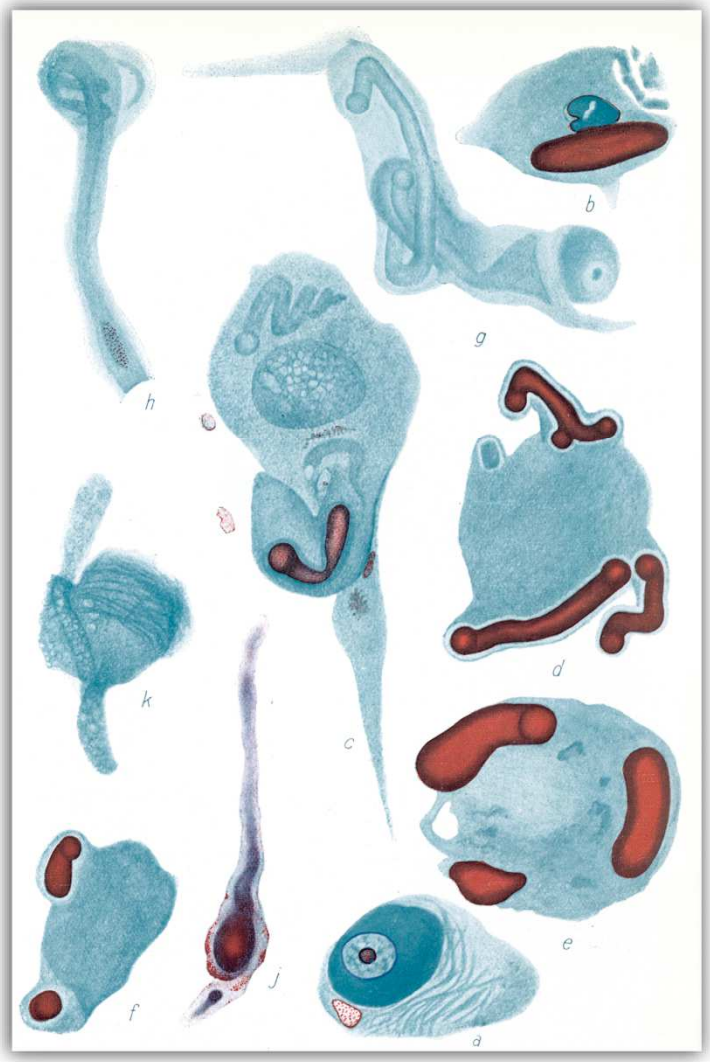
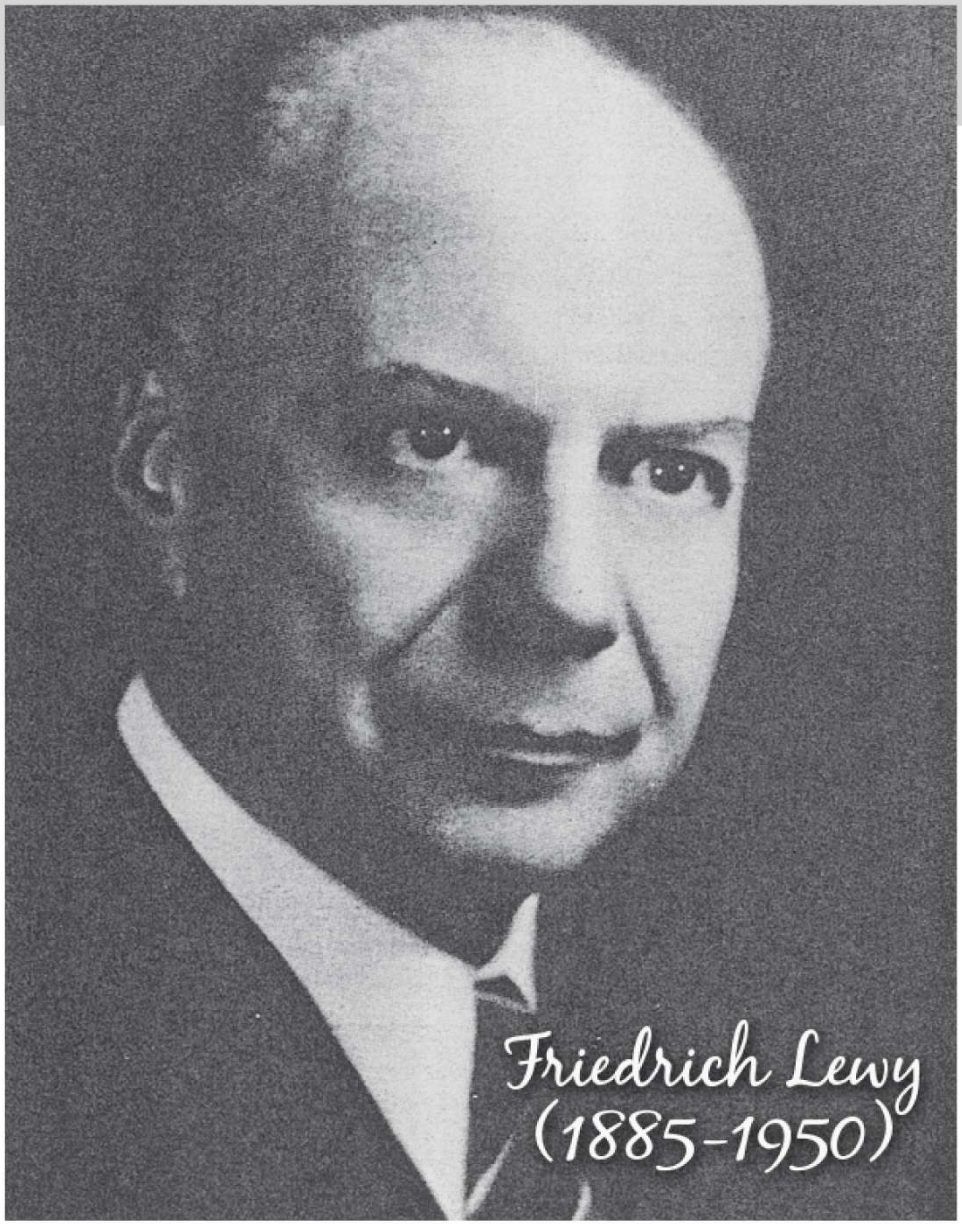
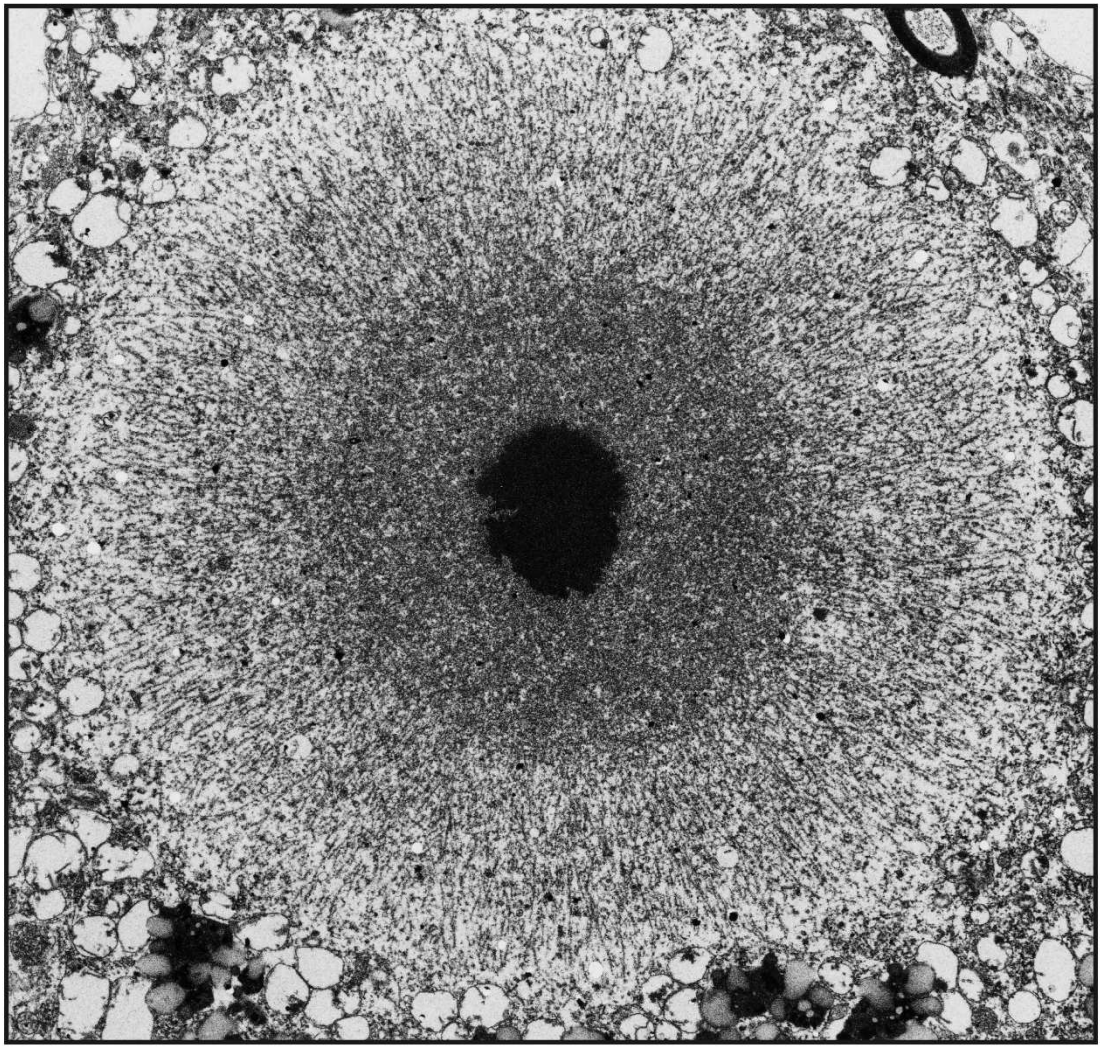
Lewy Pathology



Lewy, 1912


Friedrich Lewy
(1885-1950)

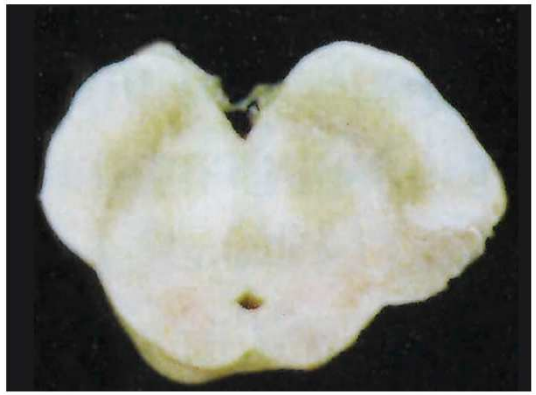
Lewy pathology filaments



Forno, 1996

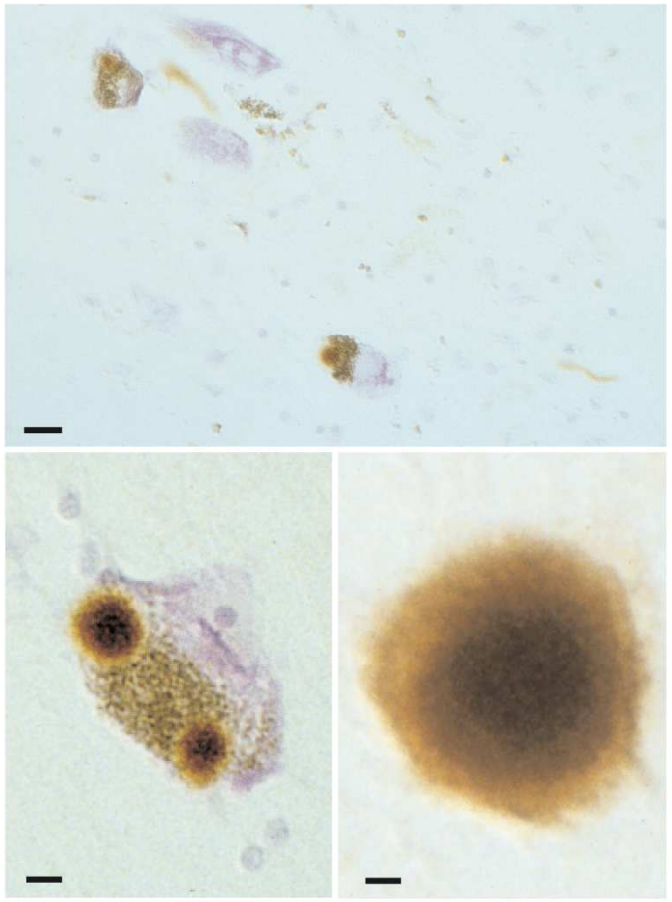
Parkinson's Disease: α-synuclein

Control



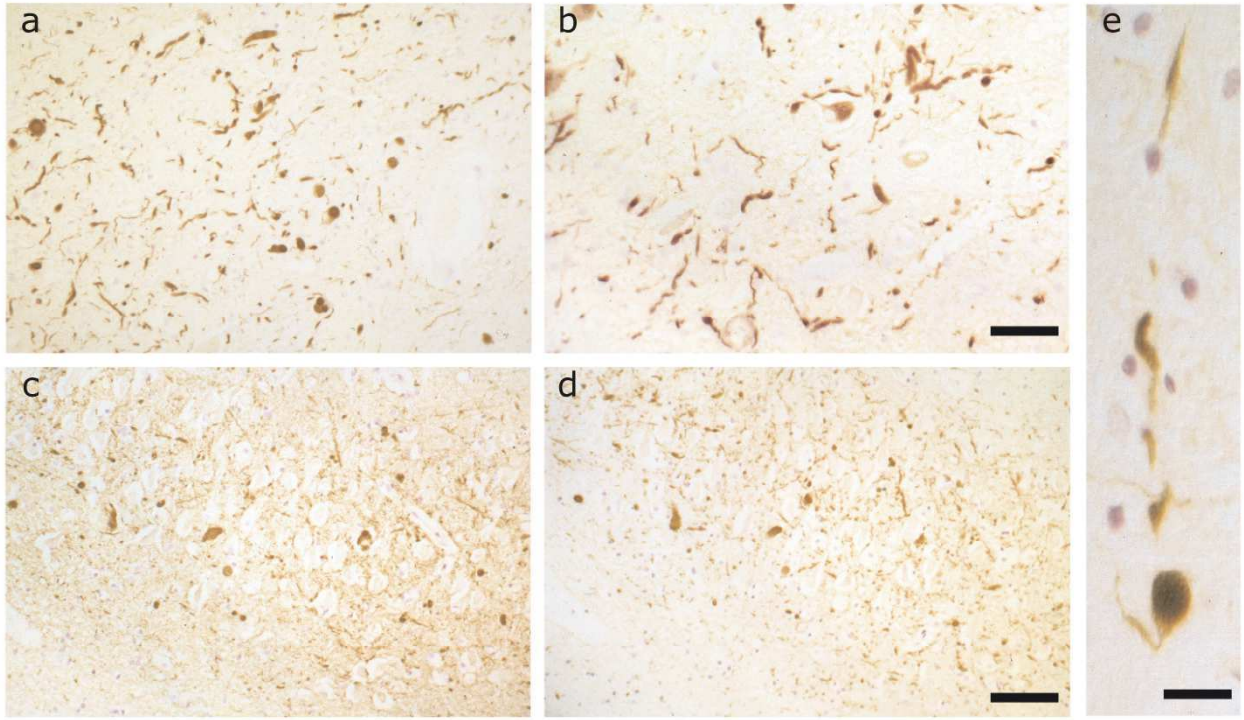
Parkinson's disease

Intracellular assembly of α synuclein



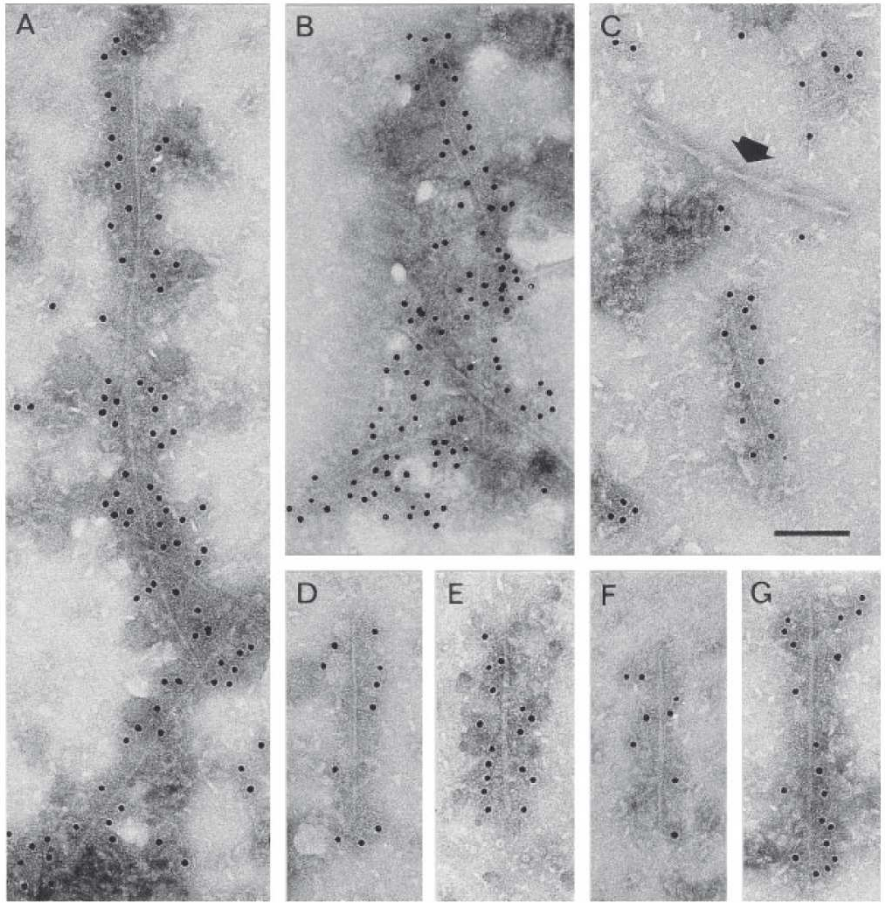
Spillantini et al., 1997

Dementia with Lewy bodies: α-synuclein

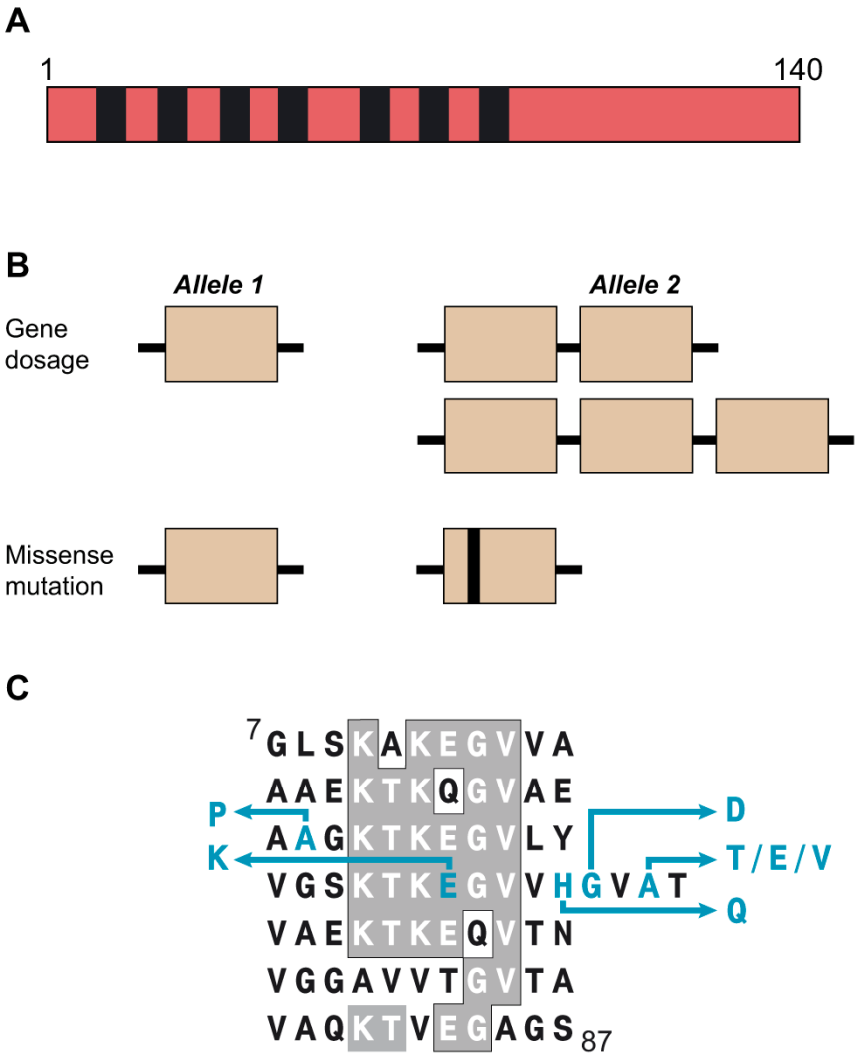


Spillantini et al., 1998a

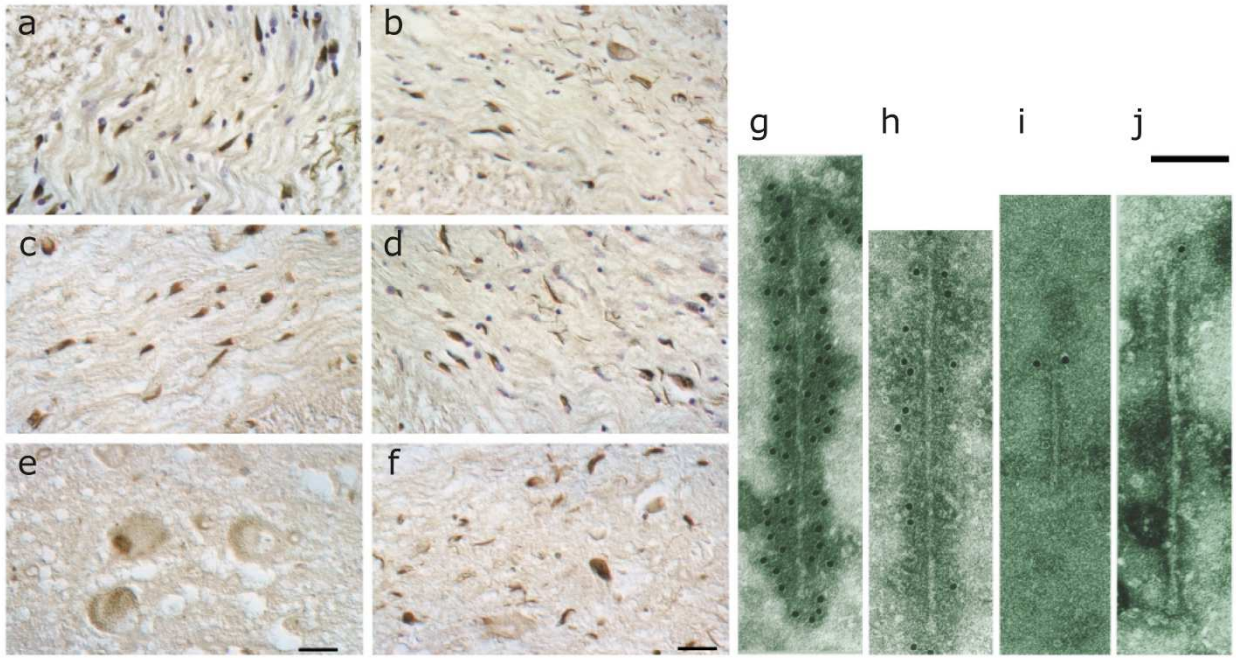
Lewy pathology filaments: α-synuclein



SCNA mutations cause Parkinson's disease and dementia with Lewy bodies



Multiple system atrophy: α-synuclein



Spillantini et al., 1998b

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Prion diseases

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No mechanism-based therapies

Plaques and Tangles

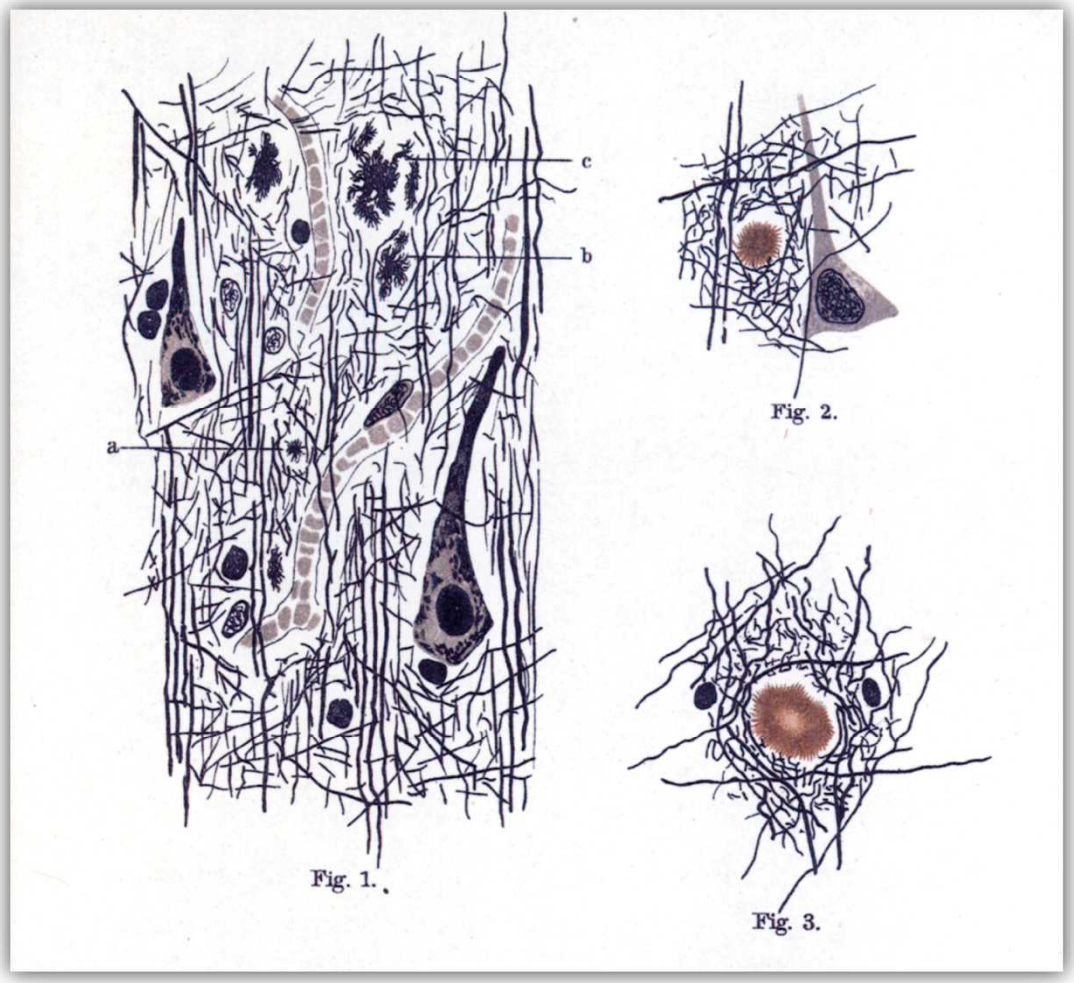
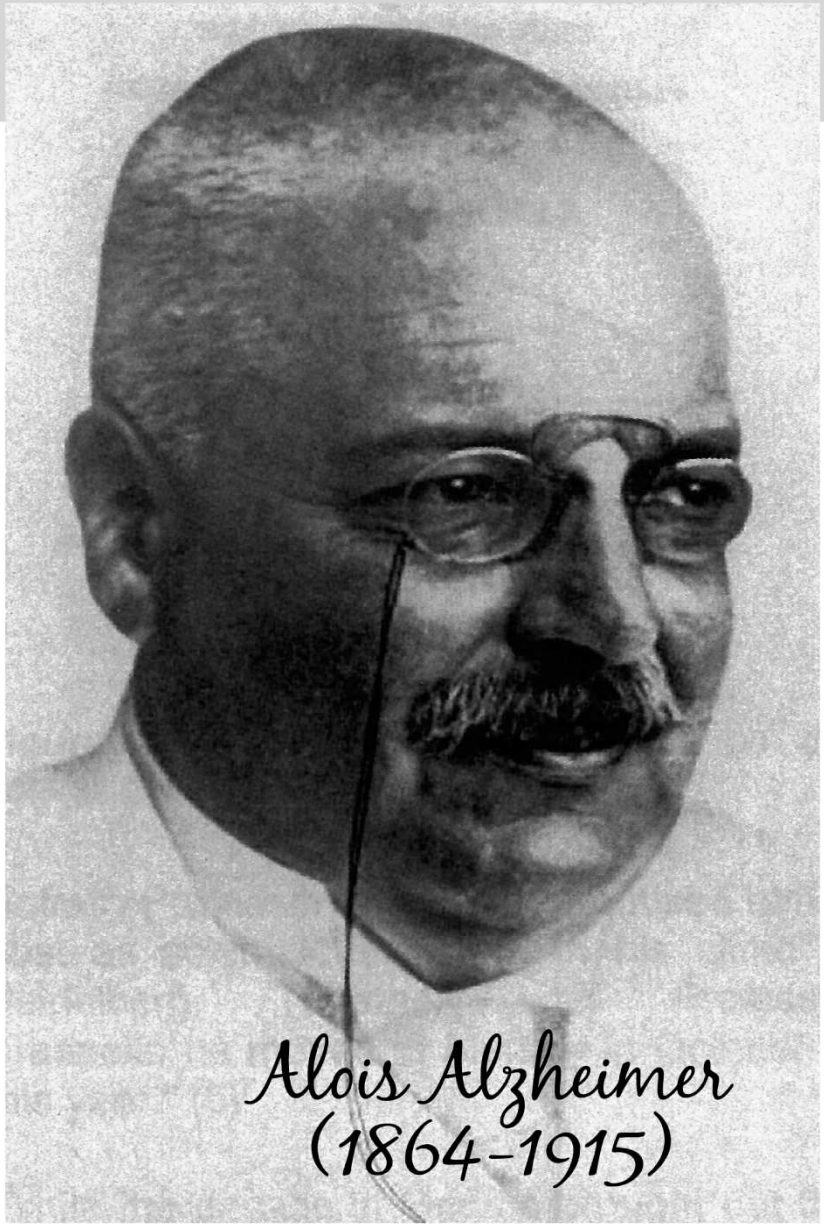


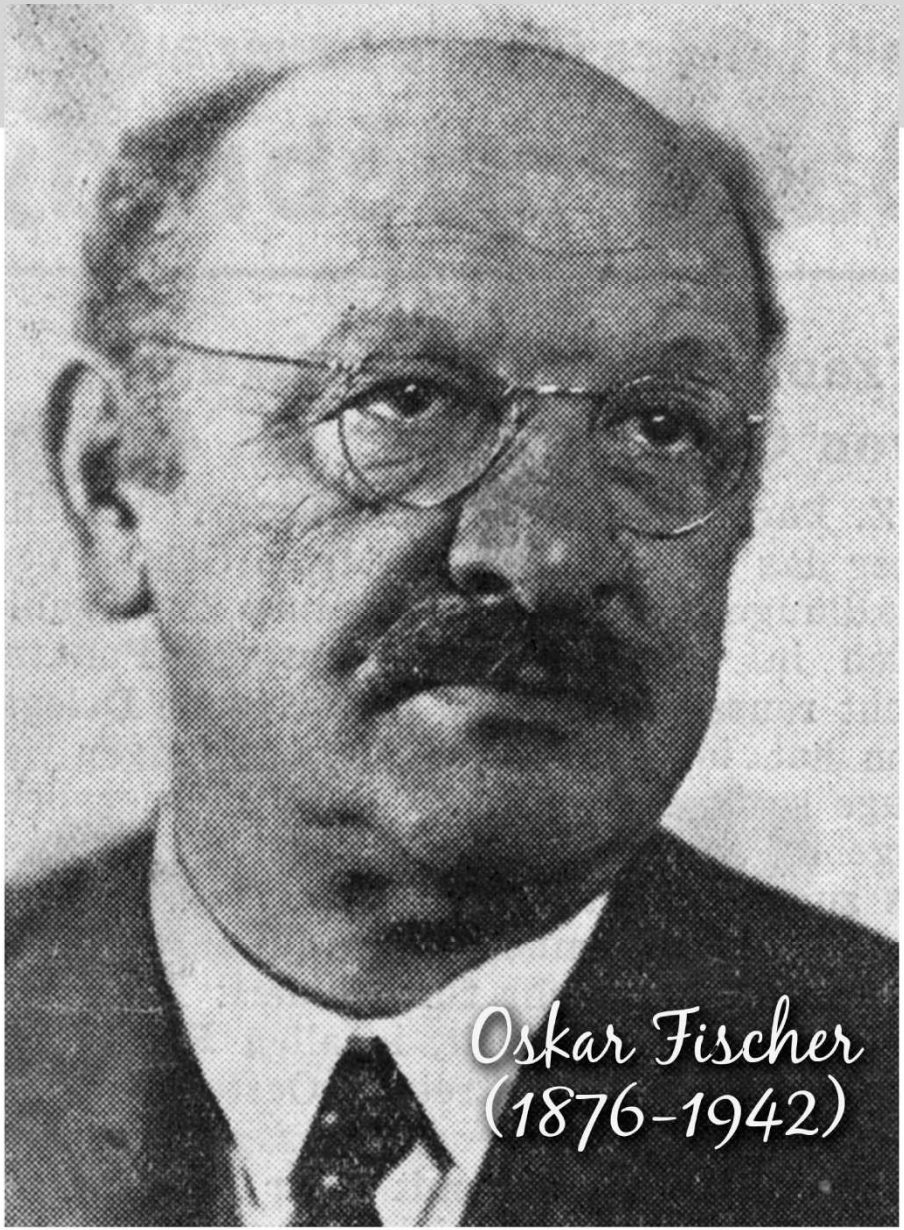
Fig. 1.

Fig. 2.

Fig. 3.

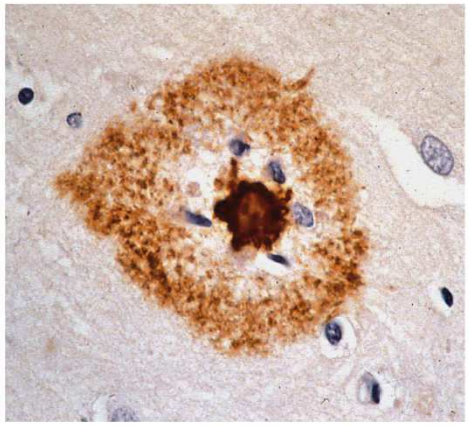
Alzheimer, 1907
Fischer, 1907

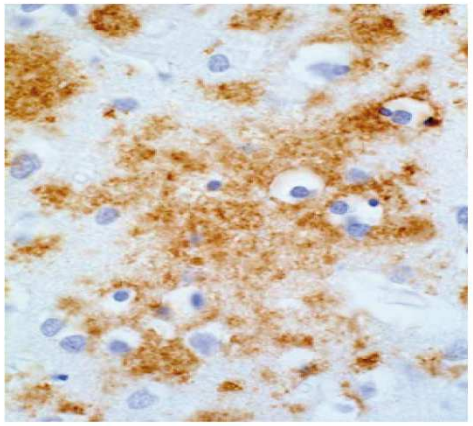

Alois Alzheimer
(1864-1915)

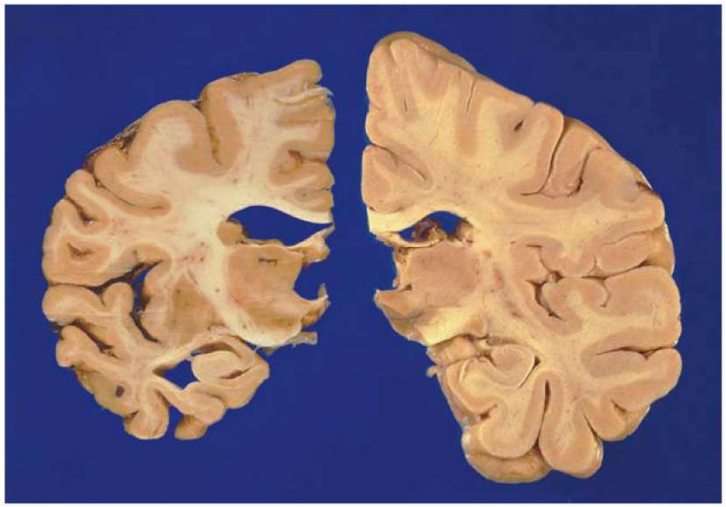

Oskar Fischer
(1876-1942)

Alzheimer's Disease: Beta-Amyloid and Tau

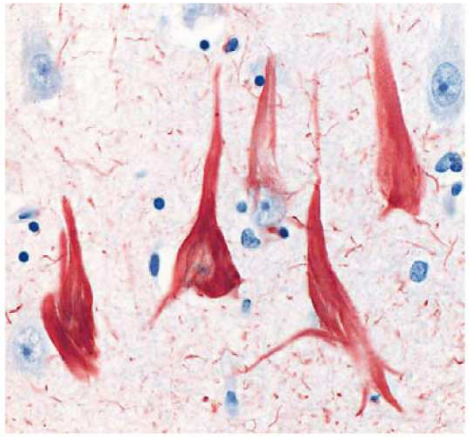
Extracellular deposition of β-amyloid

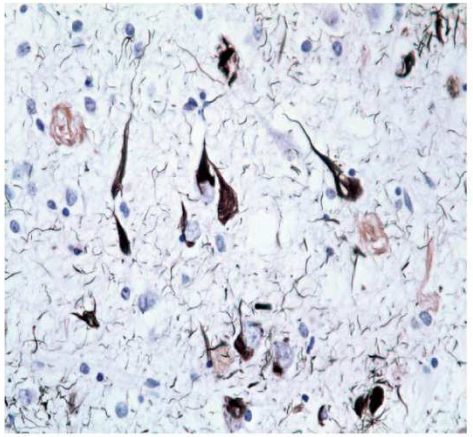




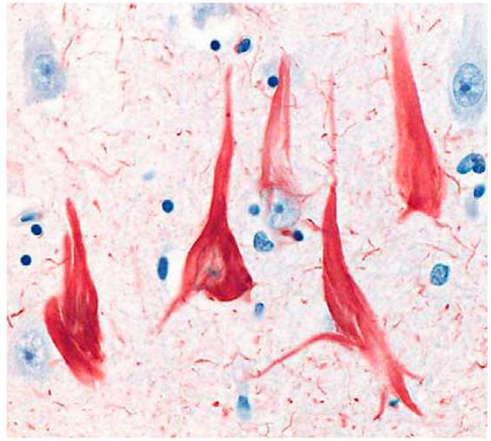


Intracellular assembly of tau protein

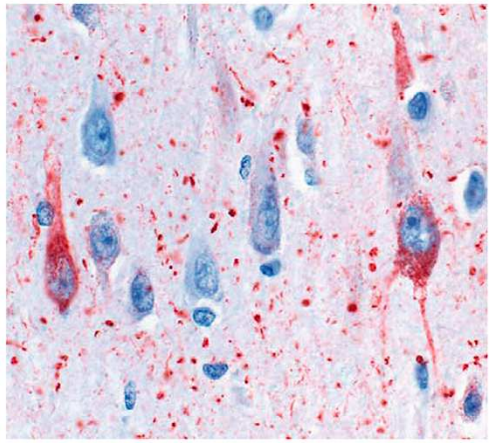




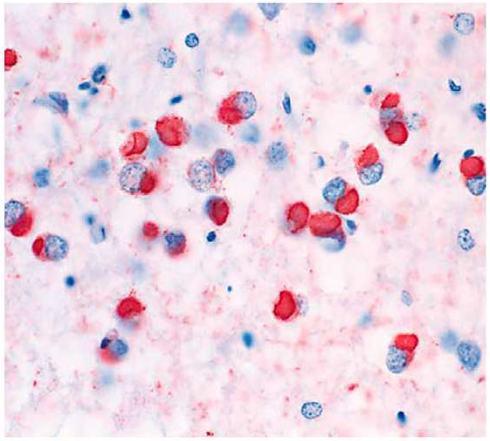
Neuropathological Spectrum of Tauopathies



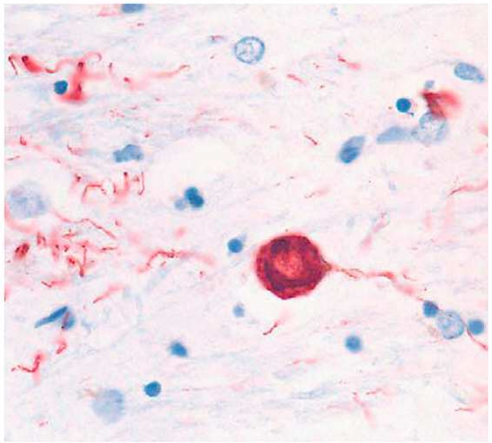
Alzheimer's disease



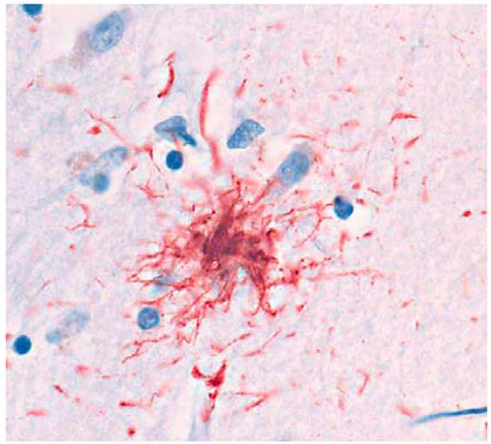
Argyrophilic grain disease

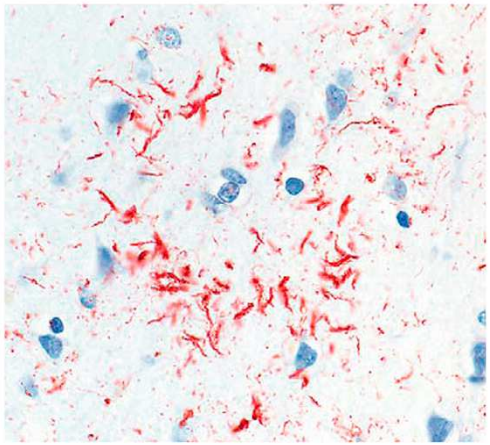


Pick's disease



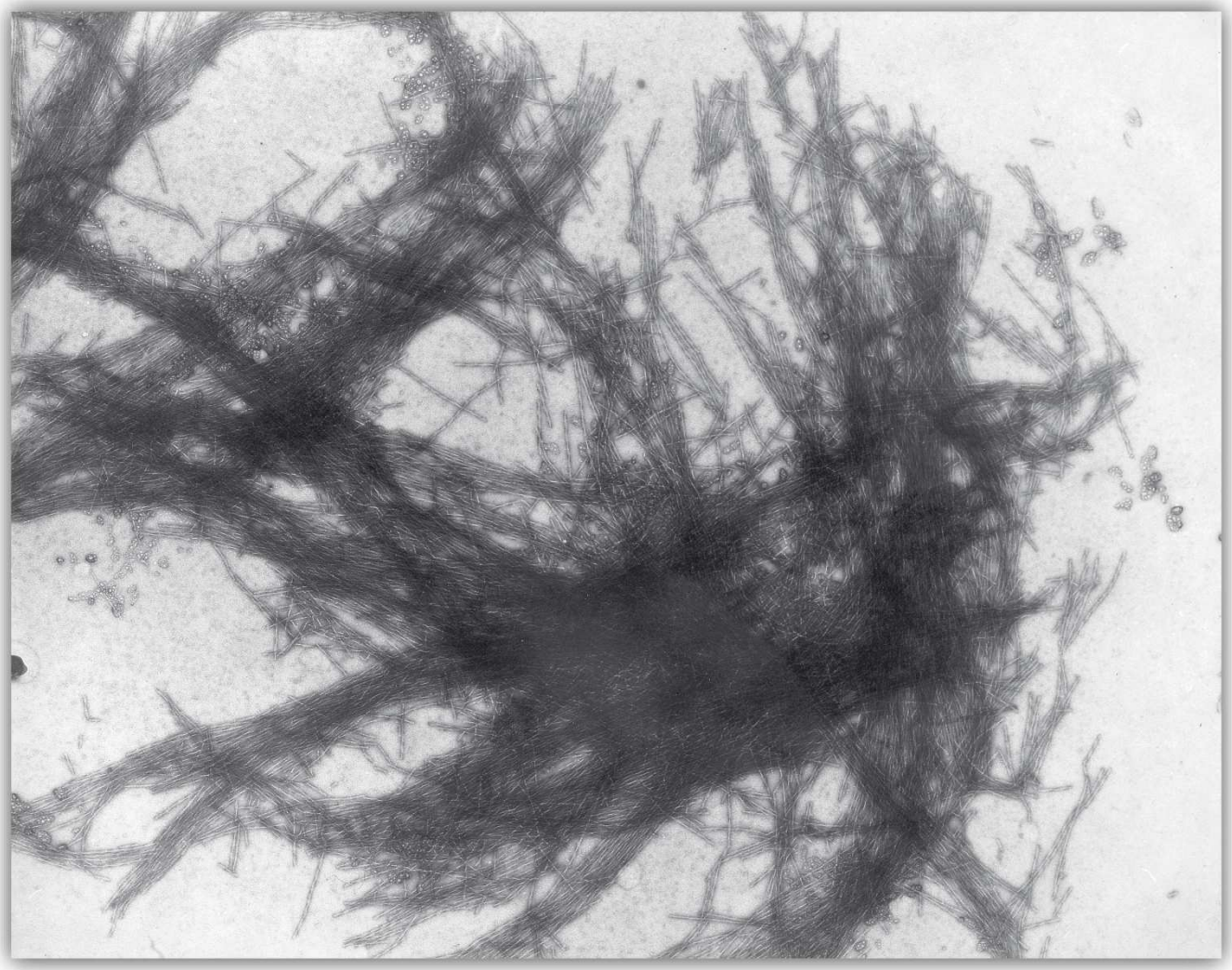
Progressive supranuclear palsy





Corticobasal degeneration

Abnormal Filaments



Cloning and sequencing of the cDNA encoding a core protein of the paired helical filament of Alzheimer disease: Identification as the microtubule-associated protein tau

(molecular pathology/neurodegenerative disease/neurofibrillary tangles)

M. GOEDERT*, C. M. WISCHIK*†, R. A. CROWTHER*, J. E. WALKER*, AND A. KLUG*

*Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, United Kingdom; and †Department of Psychiatry, University of Cambridge Clinical School, Hills Road, Cambridge CB2 2QQ, United Kingdom

PNAS (1988) 85, 4051-4055

Tau Is a Candidate Gene for Chromosome 17 Frontotemporal Dementia

Parvoneh Poorkaj, PhD,*† Thomas D. Bird, MD,*‡ Ellen Wijsman, PhD,§¶‖ Ellen Nemens, MS,* Ralph M. Garruto, PhD,# Leojean Anderson, BS,* Athena Andreadis, PhD,** Wigbert C. Wiederholt, MD,†† Murray Raskind, MD,‡‡§§ and Gerard D. Schellenberg, PhD*†‡¶¶

Annals of Neurology (1998) 44, 815-825

Association of missense and 5′-splice-site mutations in *tau* with the inherited dementia FTDP-17

Mike Hutton*[1], Corinne L. Lendon*[2], Patrizia Rizzu*[3,4], Matt Baker[1], Susanne Froelich[3,5], Henry Houlden[1], Stuart Pickering-Brown[6], Sumi Chakraverty[2], Adrian Isaacs[1], Andrew Grover[1], Jennifer Hackett[1], Jennifer Adamson[1], Sarah Lincoln[1], Dennis Dickson[1], Peter Davies[7], Ronald C. Petersen[8], Martijn Stevens[4], Esther de Graaff[3], Erwin Wauters[3], Jeltje van Baren[3], Marcel Hillebrand[3], Marijke Joosse[3], Jennifer M. Kwon[9], Petra Nowotny[2], Lien Kuei Che[2], Joanne Norton[9], John C. Morris[9], Lee A. Reed[10], John Trojanowski[10], Hans Basun[5], Lars Lannfelt[5], Michael Neystat[11], Stanley Fahn[11], Francis Dark[12], Tony Tannenberg[13], Peter R. Dodd[14], Nick Hayward[15], John B. J. Kwok[16], Peter R. Schofield[16], Athena Andreadis[17], Julie Snowden[18], David Craufurd[19], David Neary[18], Frank Owen[6], Ben A. Oostra[3], John Hardy[1], Alison Goate[2], John van Swieten[4], David Mann[20], Timothy Lynch[11] & Peter Heutink[3]

* *These authors contributed equally to this work*

Nature (1998) 393, 702-705

Mutation in the tau gene in familial multiple system tauopathy with presenile dementia

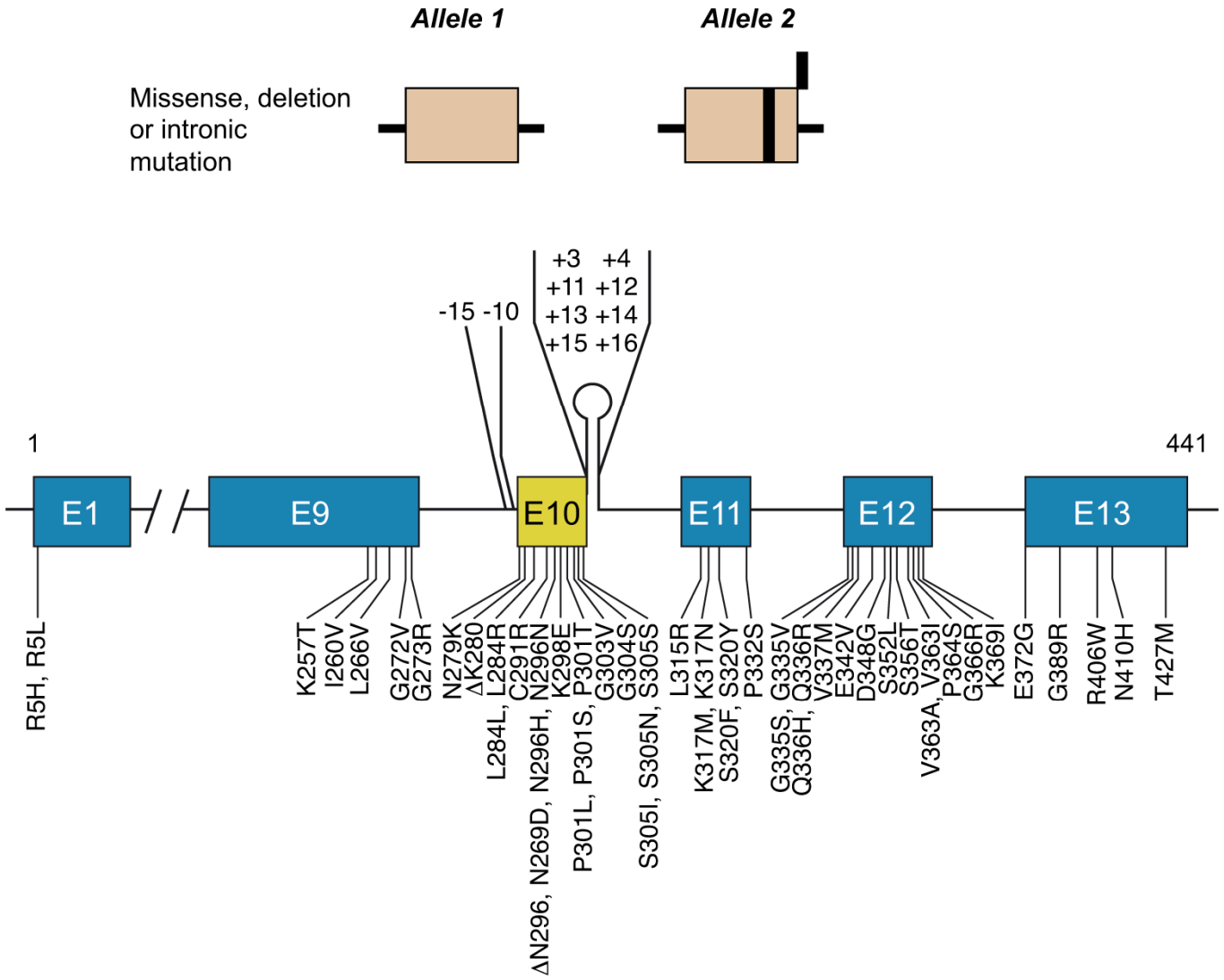
alternative mRNA splicing/Four-repeat tau isoforms/Frontotemporal dementia/microtubule binding/Tau filaments

MARIA GRAZIA SPILLANTINI*†‡, JILL R. MURRELL†§, MICHEL GOEDERT¶, MARTIN R. FARLOW§, AARON KLUG¶, AND BERNARDINO GHETTI§

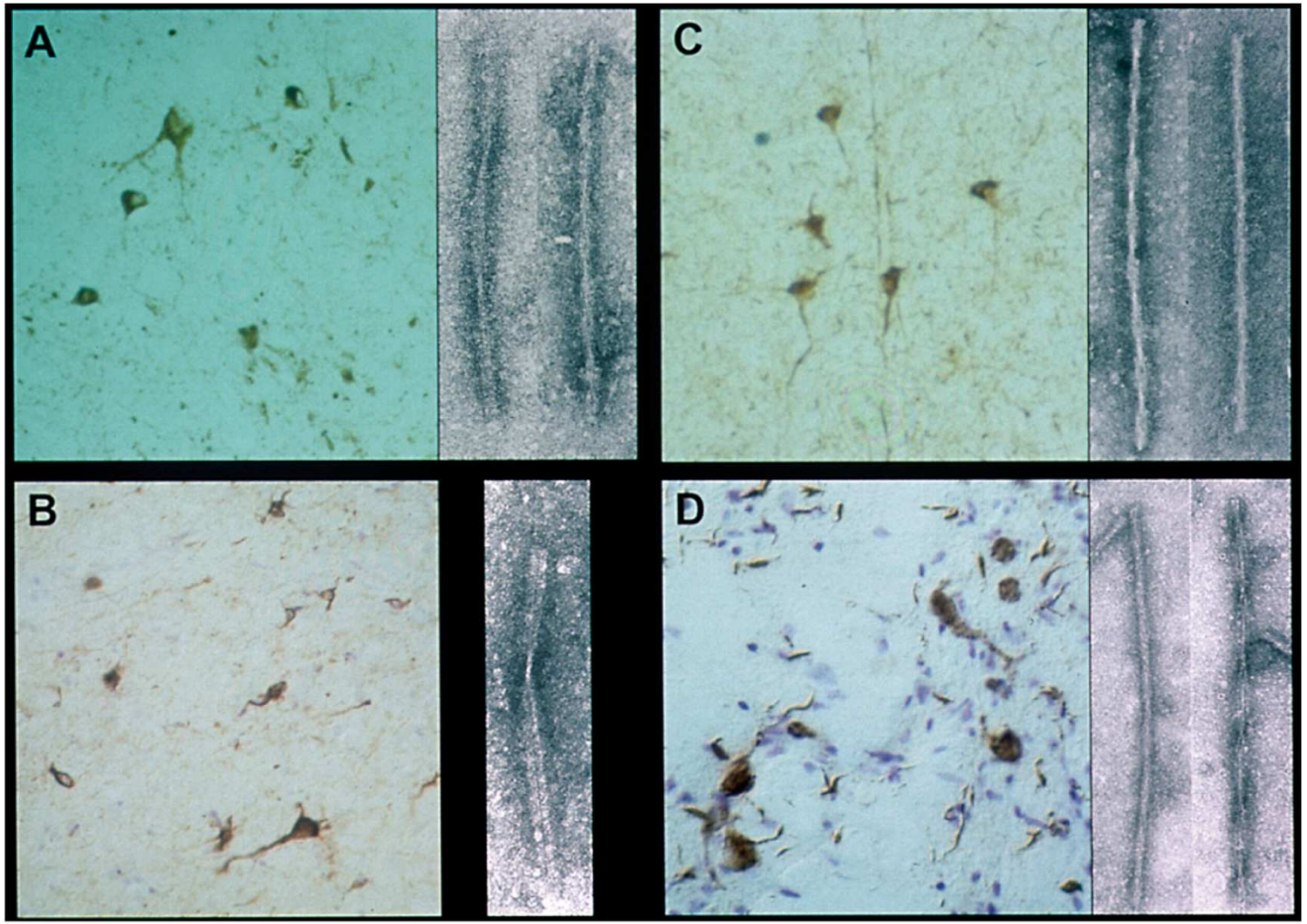
*Medical Research Council Centre for Brain Repair and Department of Neurology, University of Cambridge, Robinson Way, Cambridge CB2 2PY, U.K.; §Departments of Pathology and Laboratory Medicine (Division of Neuropathology) and Neurology, Indiana University School of Medicine, Indianapolis, IN 47202; and ¶Medical Research Council Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH, U.K.

PNAS (1998) 95, 7737-7741

MAPT mutations cause FTLD

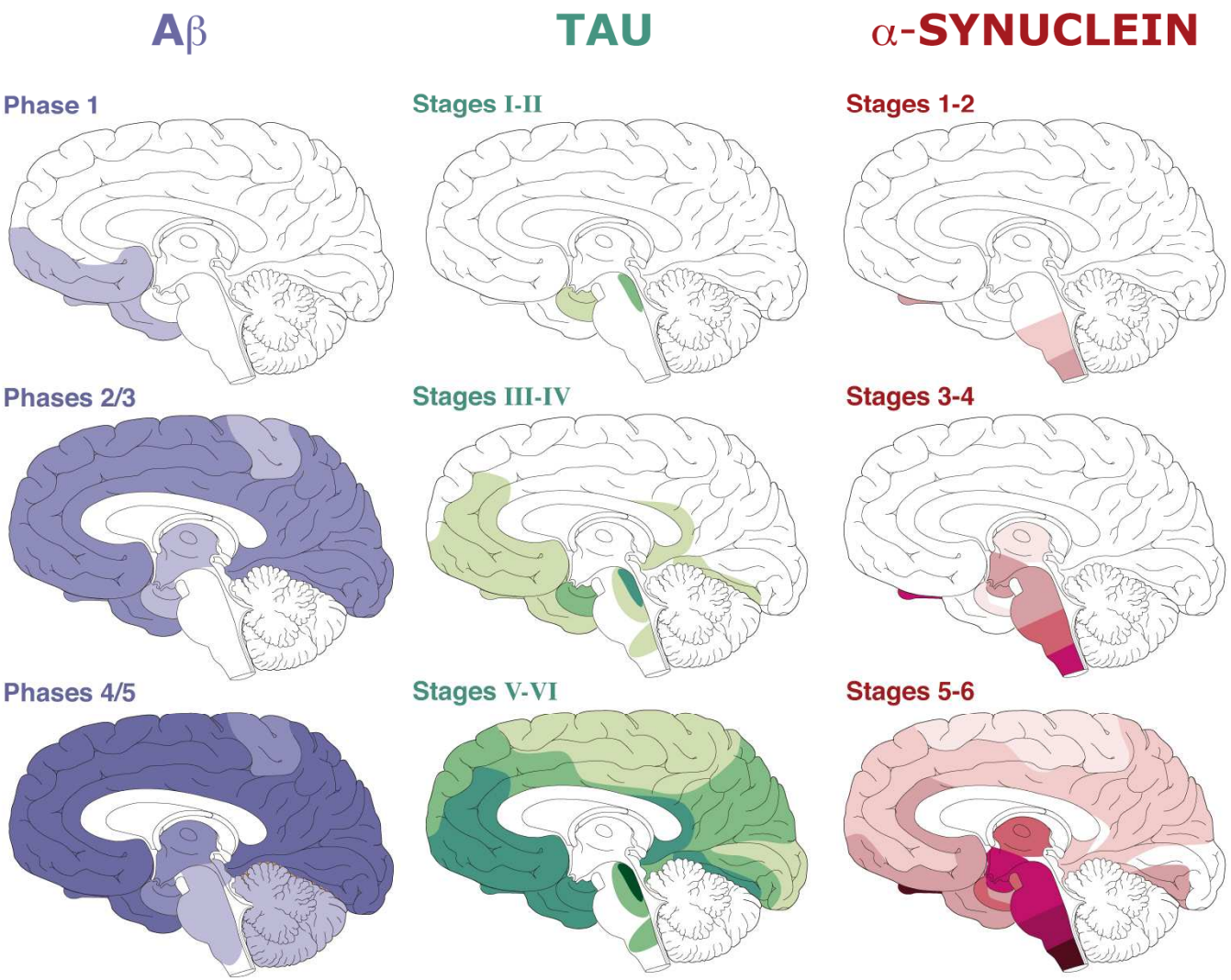


FTLD pathologies



In Alzheimer’s disease the ordered assembly of Tau into filaments is linked to neurodegeneration and cognitive impairment.

Spreading of Aβ, tau and α-synuclein inclusions

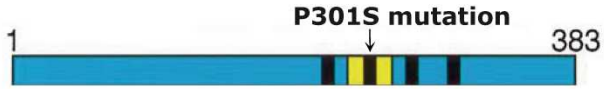


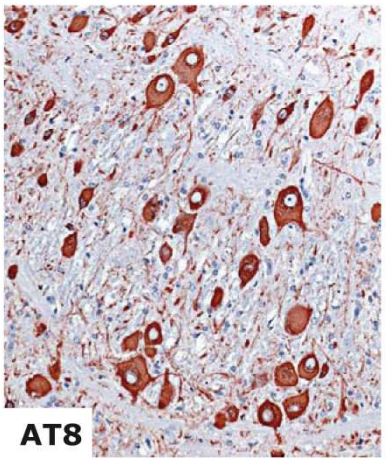
Braak &
Del Tredici,
2009, 2015

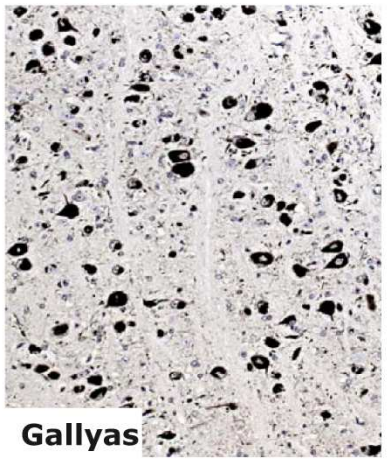
P301S and Alz17 Tau Transgenic Mice

P301S mouse

Allen et al., J Neurosci 2002



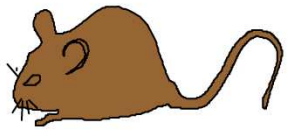


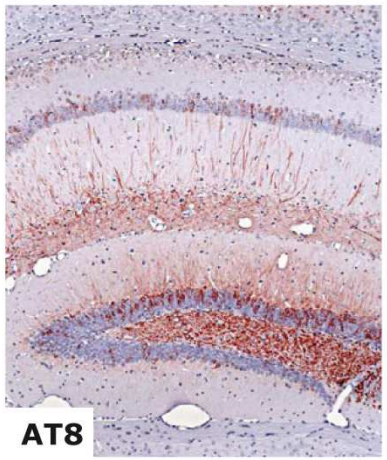


- **Expression of P301S mutant human tau**
- **Thy-1.2 promoter**
- **Robust tangle pathology**
- **Insoluble, filamentous tau (Gallyas silver staining)**

Alz17 mouse

Götz et al., EMBO J 1995
Probst et al., Acta Neuropathol 2000

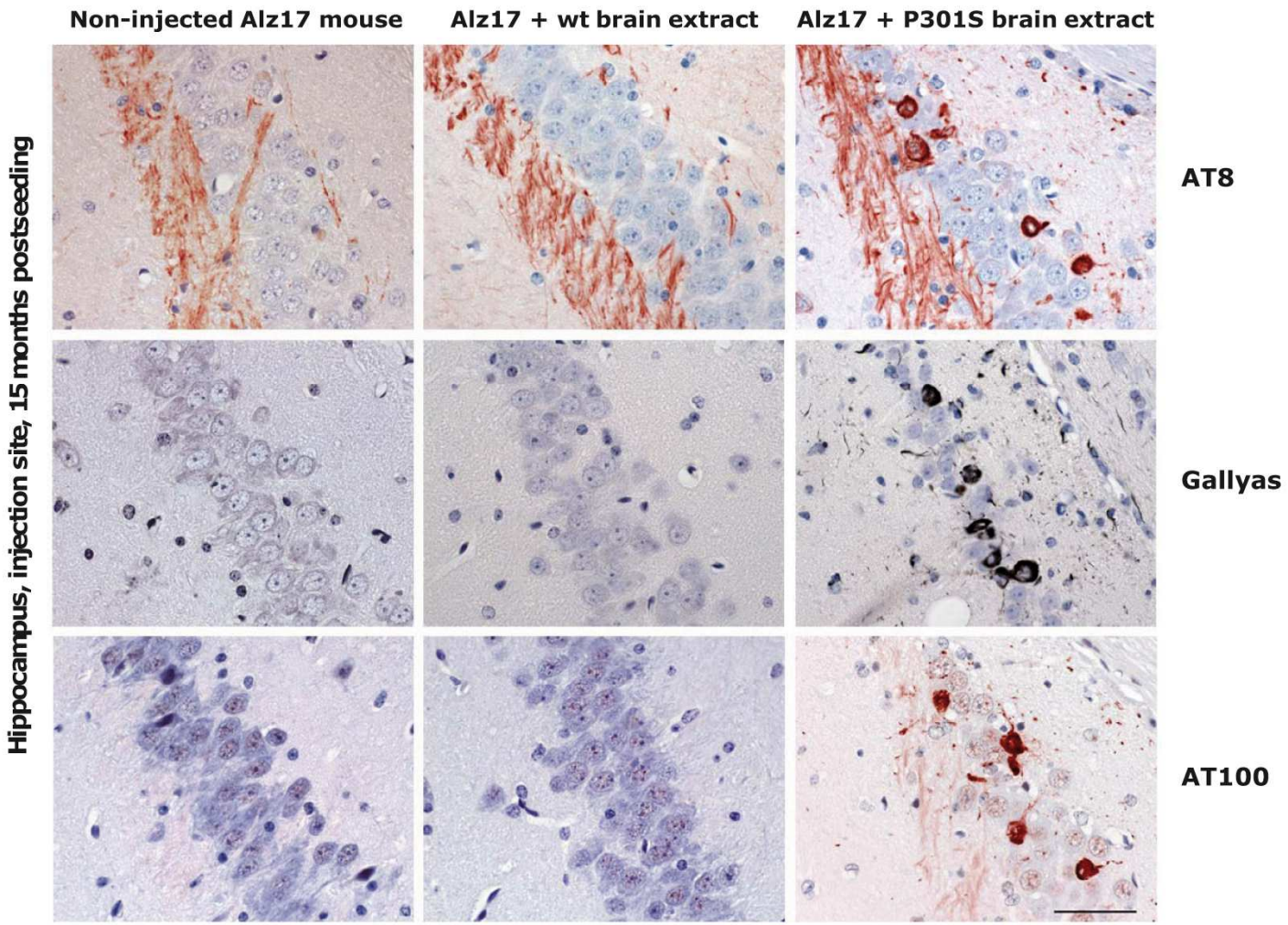




- **Expression of wild-type human tau**
- **Thy-1.2 promoter**
- **Robust pre-tangle pathology**
- **Soluble, no filamentous tau (no Gallyas silver staining)**

Clavaguera et al., 2009

Induction of Filamentous Tau Pathology in Alz17 Mice



Semi-quantitative grading of filamentous tau pathology

Anterior (1.7 mm from injection level)

	Time after injection (months)		
Region	6	12	15
Fimbria	++	+++	+++
Thalamus	+	++	++
Internal capsule	–	+	++
Caudate putamen	–	+	+
Somatosensory cortex	–	+	+
Hypothalamus	–	–	+
Amygdala	–	–	+

Injection level

	Time after injection (months)		
Region	6	12	15
Hippocampus*,[1]	++	+++	+++
Optic tract	++	++	+++
Fimbria	+	++	+++
Medial lemniscus	+	++	+++
Zona incerta	+	++	+++
Thalamus	+	++	++
Cerebral peduncle	+	++	++
Visual cortex[2]	+	+	++
Hypothalamus	+	+	+
Amygdala	–	+	+

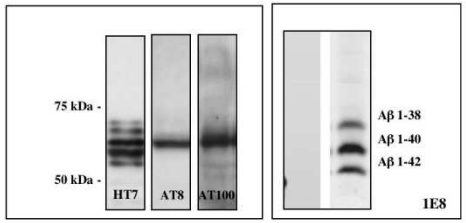
Posterior (1.3 mm from injection level)

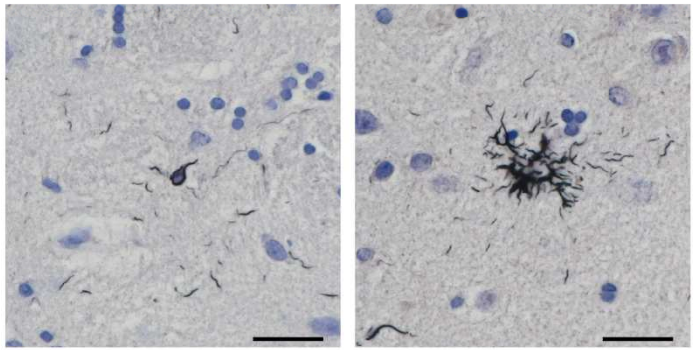
	Time after injection (months)		
Region	6	12	15
Cerebral peduncle	++	+++	+++
Hippocampus*	+	++	+++
Superior colliculus	+	++	++
Substantia nigra	+	+	+
Entorhinal cortex	–	+	++
Deep mesencephalic nucleus	–	+	++
Pontine nuclei	–	–	+

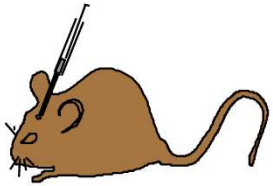
ALZ17 mice were injected with brain extract from mice transgenic for human P301S tau ($n = 5$ for each time point). – No Gallyas-Braak-positive structures; + 1–20; ++ 21–40; +++ >40; *CA1, CA2, CA3, dentate gyrus and subiculum; [1, 2]injection sites

ALZ17+PSP Human Brain Extract

Preparation of human extract

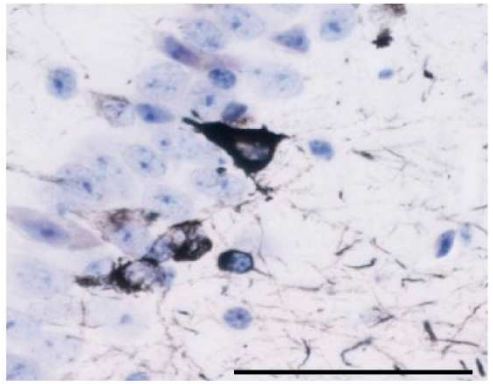


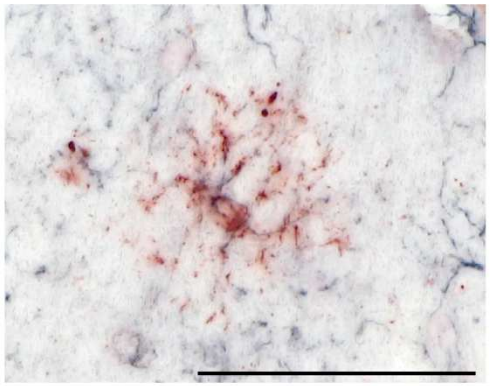


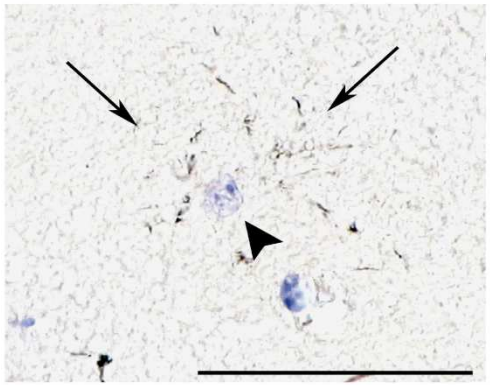


3-month-old homozygous
ALZ17 mice

Gallyas staining reveals neuronal inclusions and tufted astrocyte-like structures



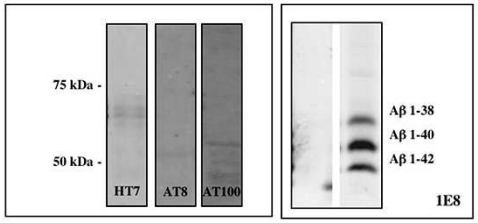


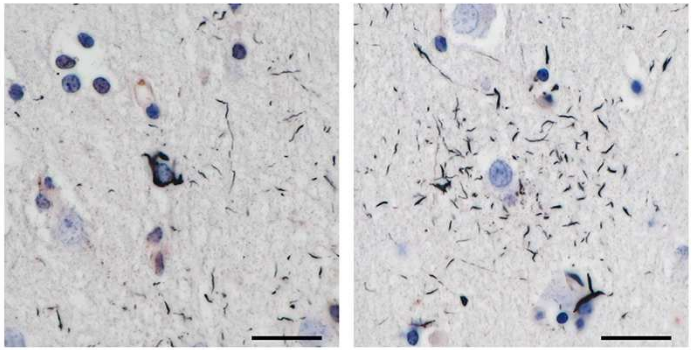


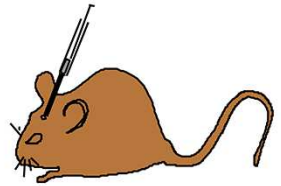
Clavaguera et al., 2013

ALZ17+CBD Human Brain Extract

Preparation of human extract

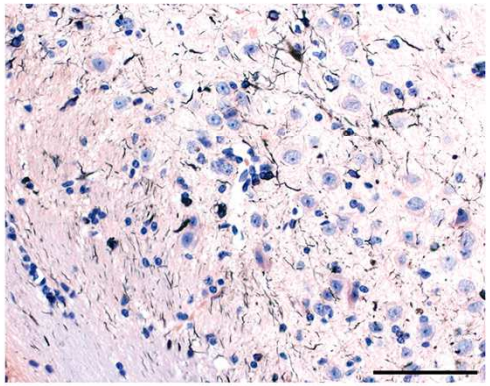


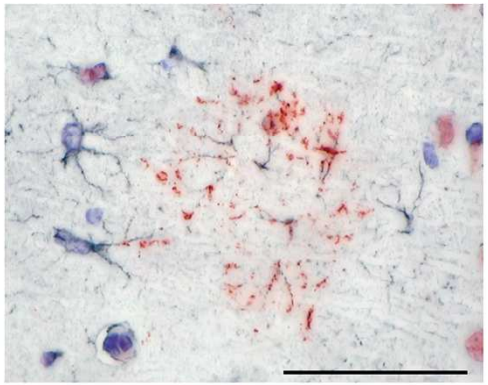


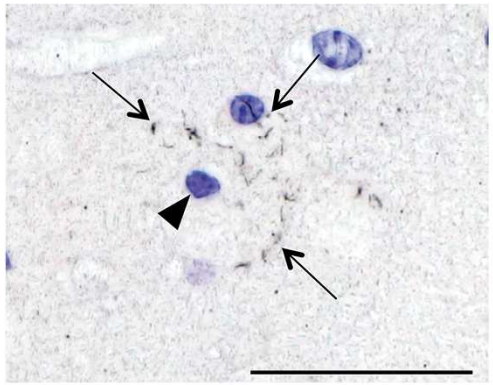


3-month-old homozygous
ALZ17 mice

Gallyas staining reveals neuronal inclusions and astrocytic plaque-like structures

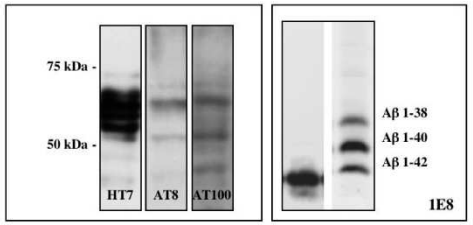


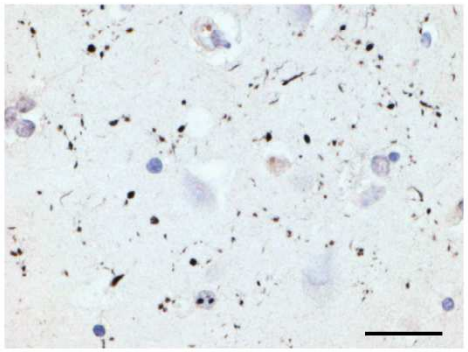


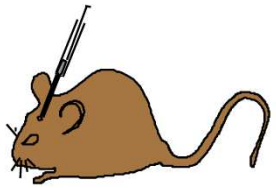


ALZ17+AGD Human Brain Extract

Preparation of human extract

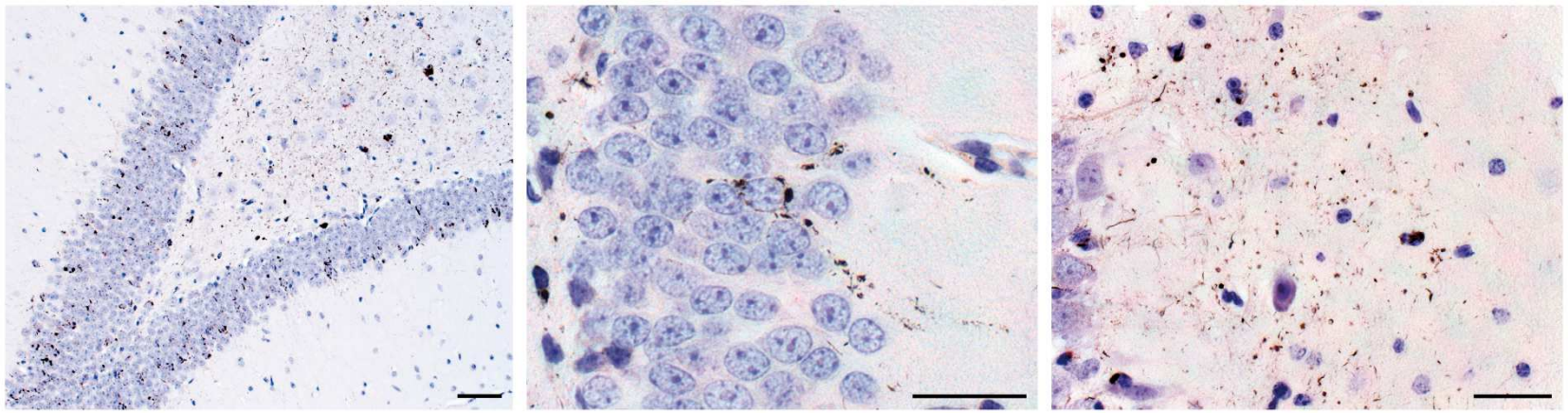






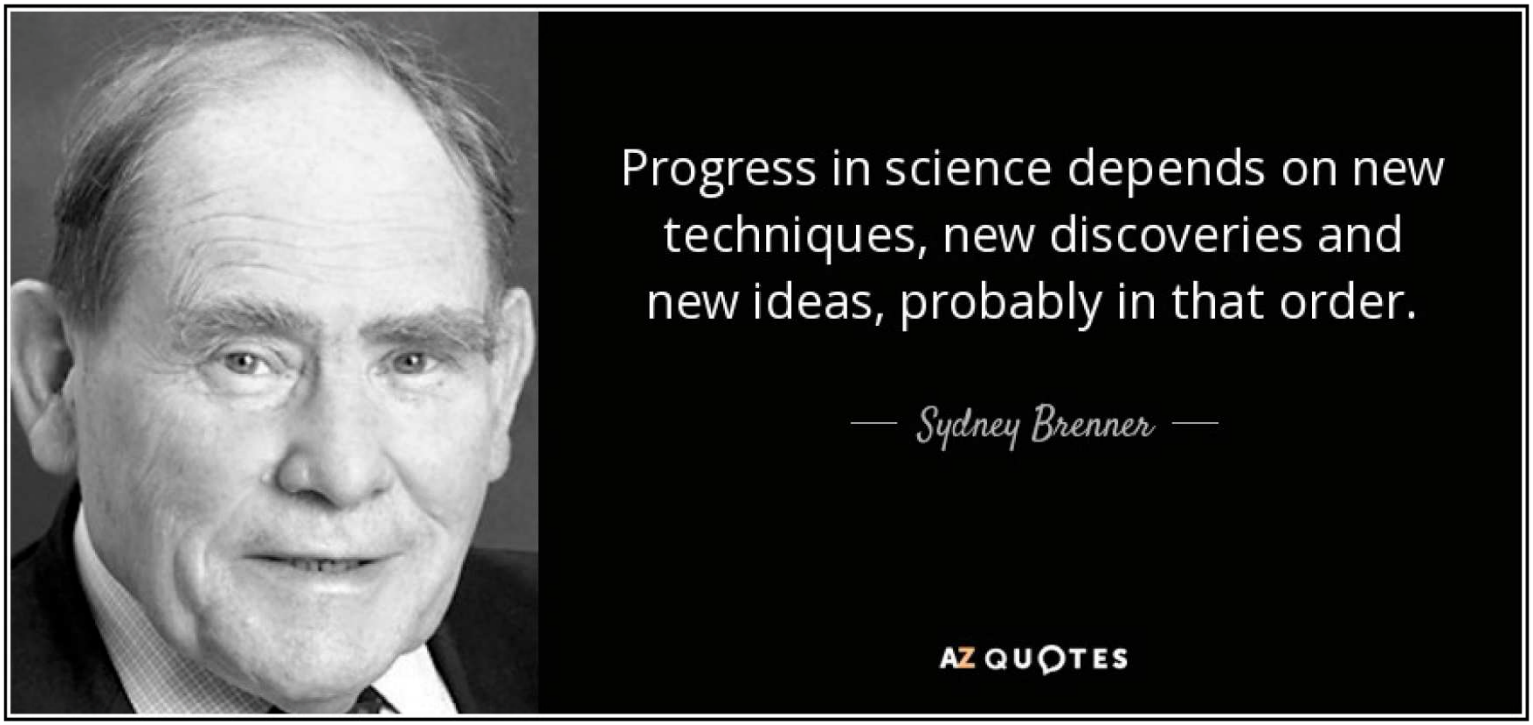
3-month-old homozygous
ALZ17 mice

Gallyas staining reveals grain-like structures



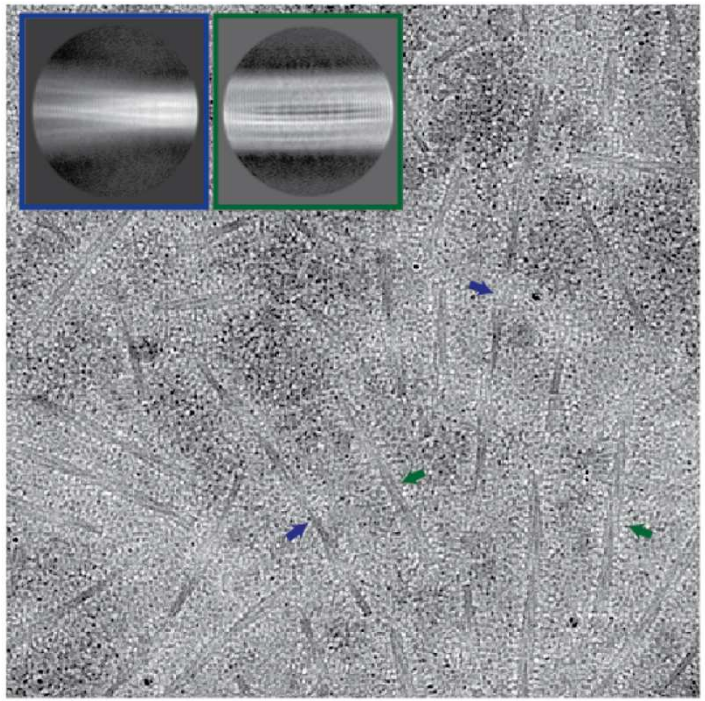
Clavaguera et al., 2013

Progress in Science



Electron Cryo-Microscopy

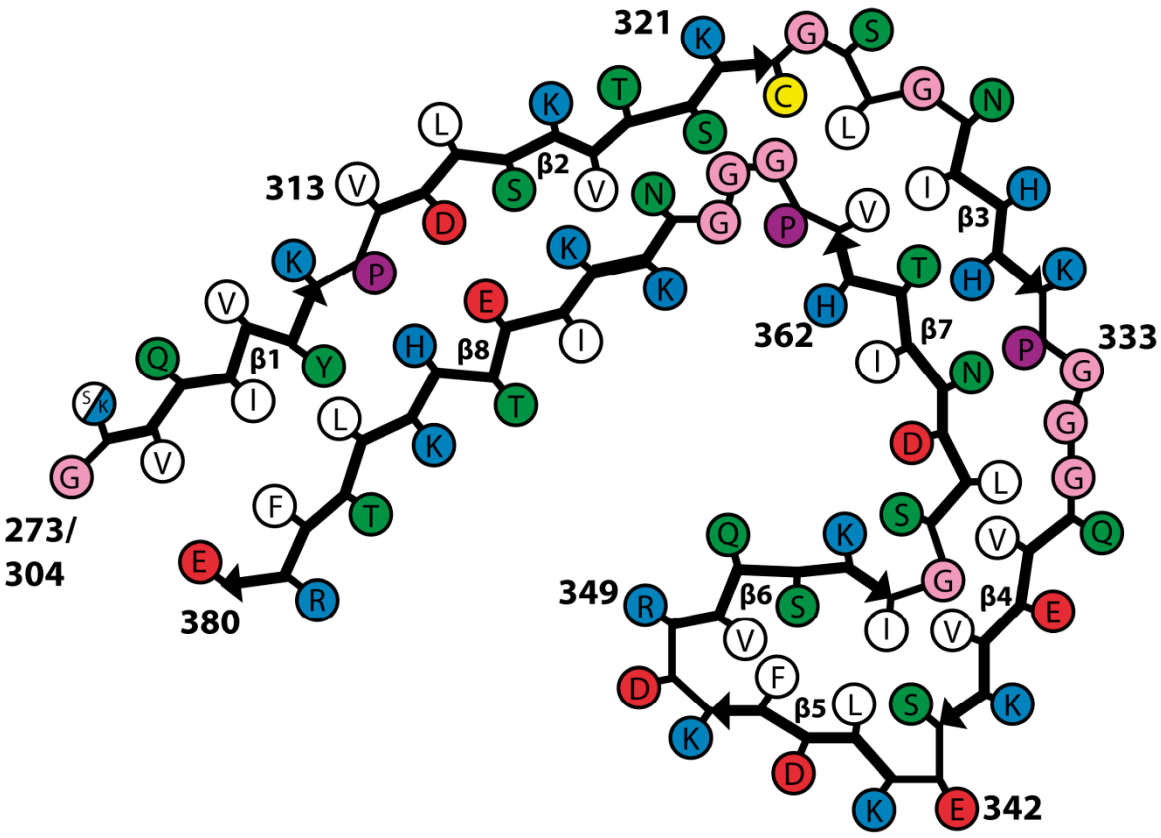
- 300kV Titan Krios, K2 detector



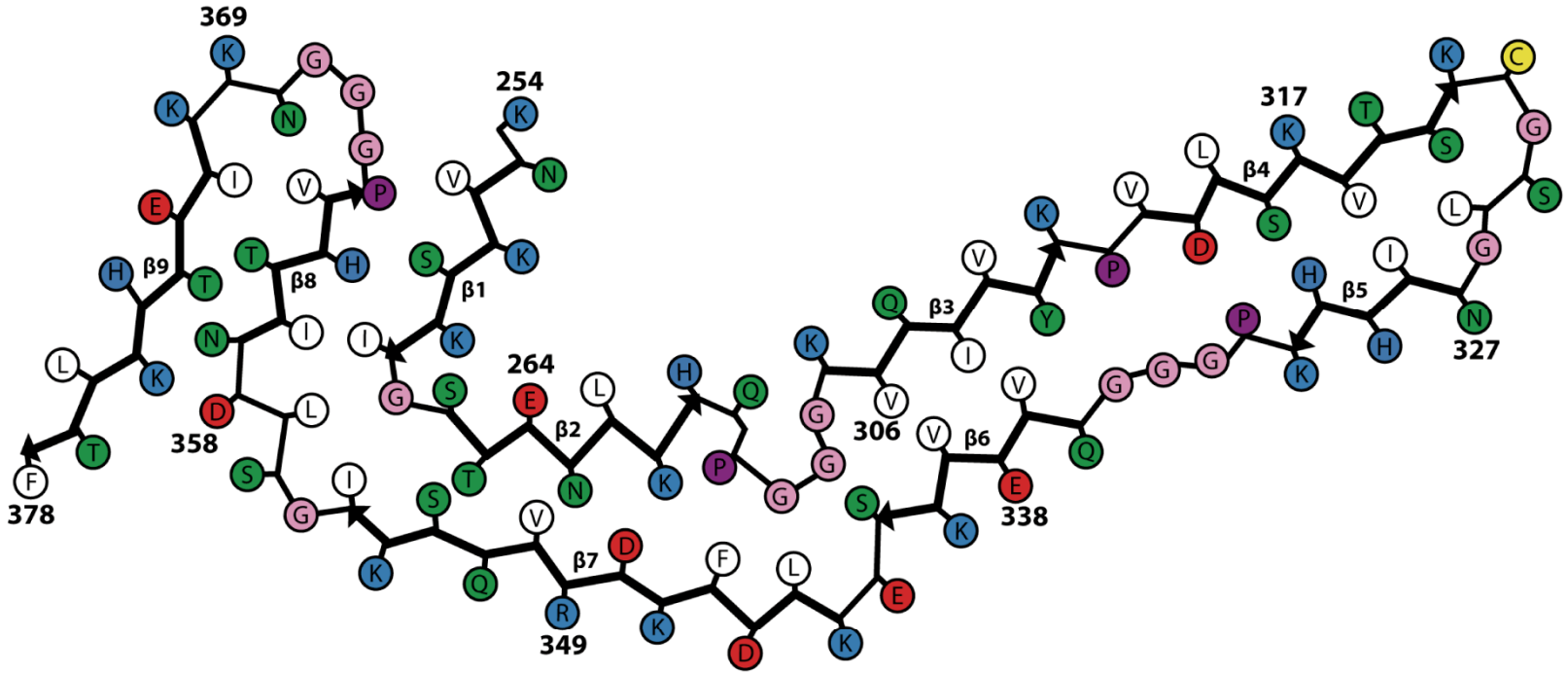
Sarkosyl-insoluble fraction

Fitzpatrick et al., 2017
Falcon et al., 2018a, b

Alzheimer fold

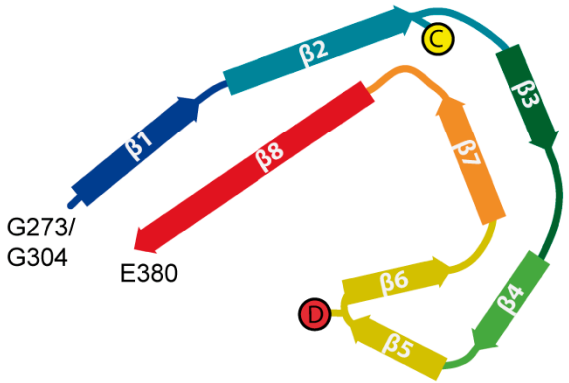


Pick fold



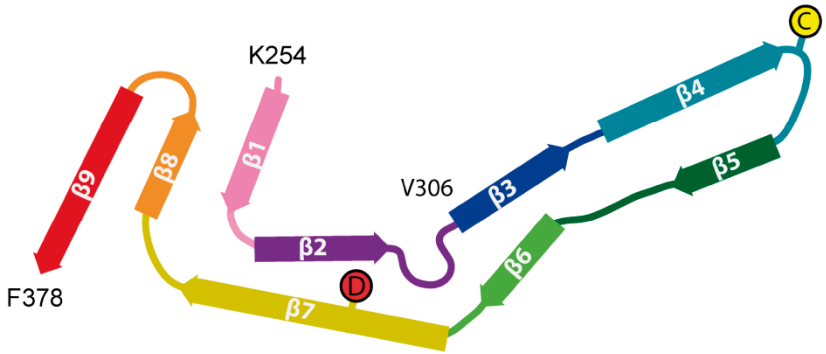
Alzheimer and Pick Folds

Alzheimer Fold



Two protofilaments

Pick Fold



Mostly one protofilament

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A. Klug
S.H.W. Scheres
M.G. Spillantini