MRC Laboratory of Molecular Biology

CJD Foundation Meeting, November 2024

Cryo-EM Structures of Amyloid Filaments from Human Brains

Michel Goedert

Neurodegenerative Diseases

Alzheimer's disease
Parkinson's disease
Dementia with Lewy bodies
Frontotemporal dementias
Progressive supranuclear palsy
Corticobasal degeneration
Chronic traumatic encephalopathy
Argyrophilic grain disease
Globular glial tauopathy
Multiple system atrophy

Sporadic and Inherited Diseases

All cases of disease (sporadic or inherited) share the presence of abundant filamentous inclusions in brain cells.

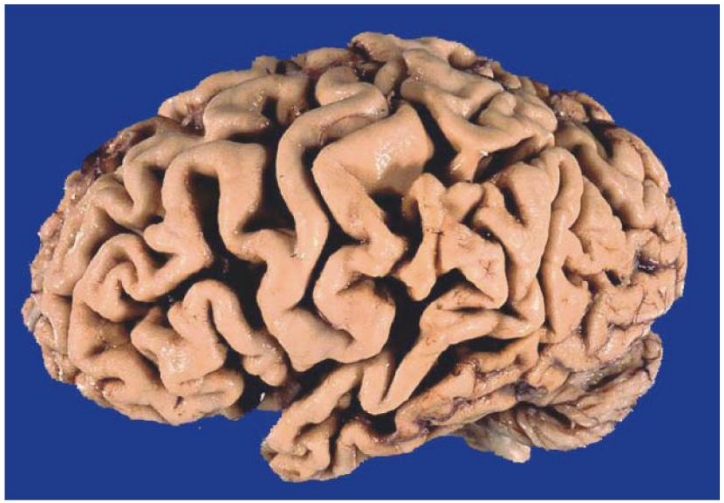
Most cases are sporadic, meaning that they happen in unpredictable ways.

Some cases (<1%) are inherited in a dominant manner, such that on average 50% of the descendants of someone with disease will develop the same disease if they live long enough.

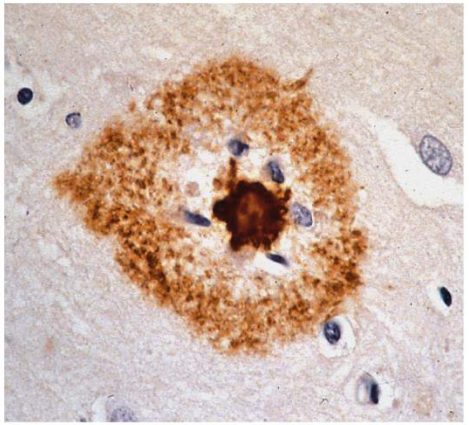
Inherited forms of disease allow one to identify causes of disease.

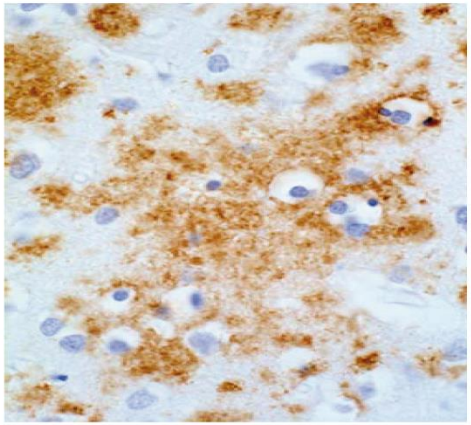
Known causes lie in changes in the genes that encode the major components of the filamentous inclusions or that increase their production. This is true of tau, APP and alpha-synuclein. It links inclusion formation and causes of disease.

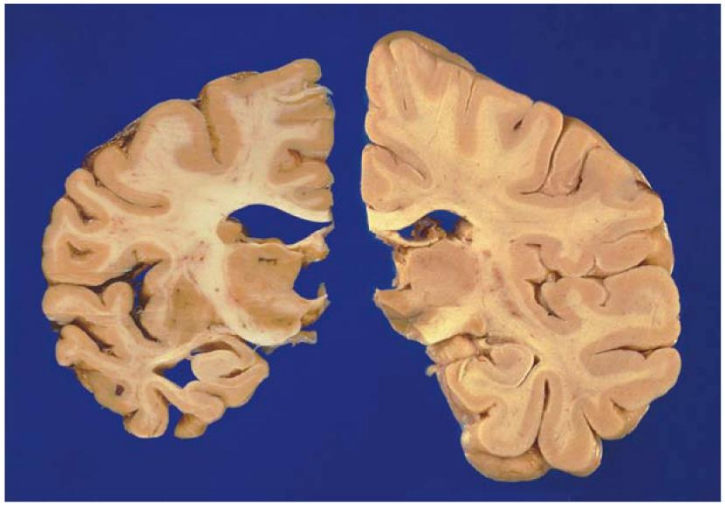
Alzheimer's Disease: Beta-Amyloid and Tau



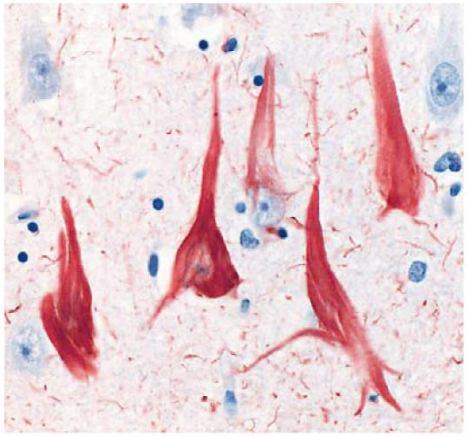
Extracellular deposition of β-amyloid

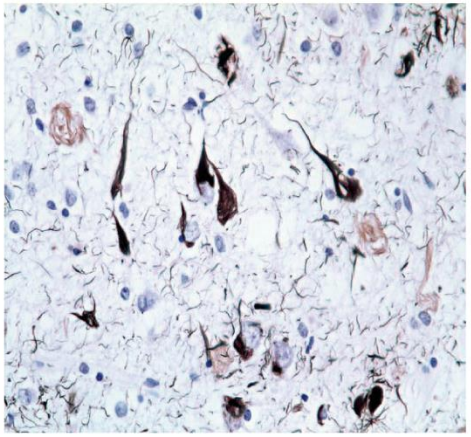




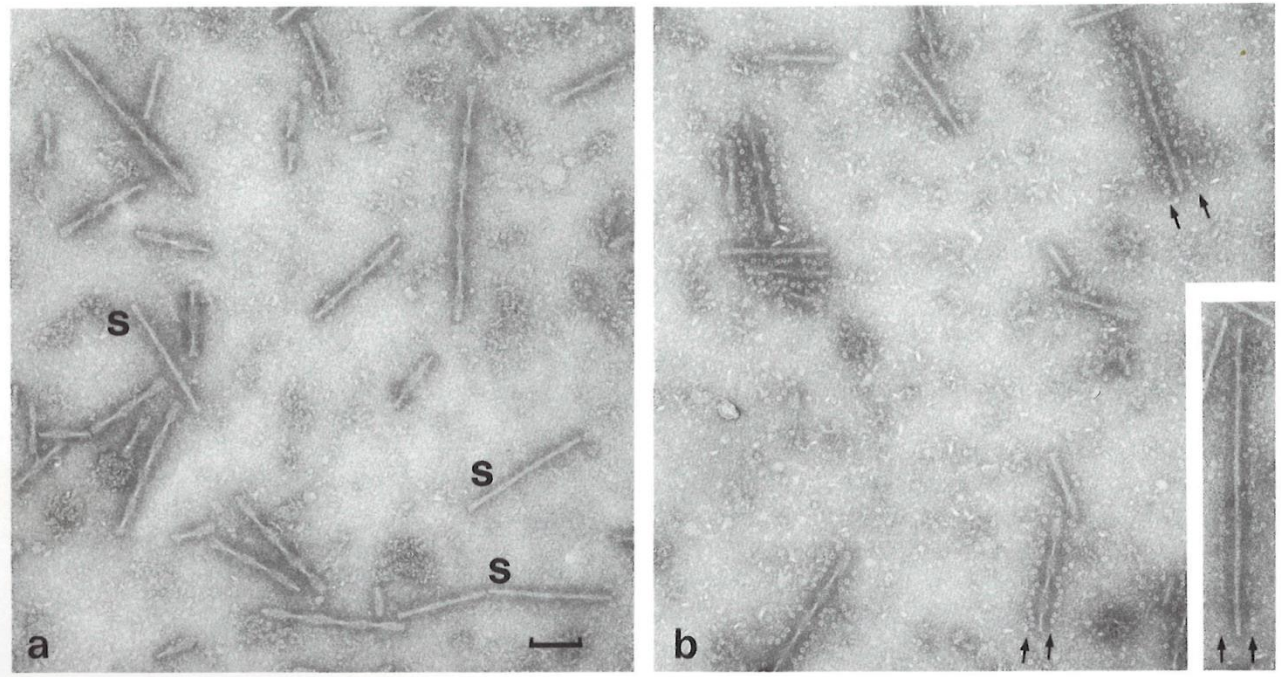


Intracellular assembly of tau protein



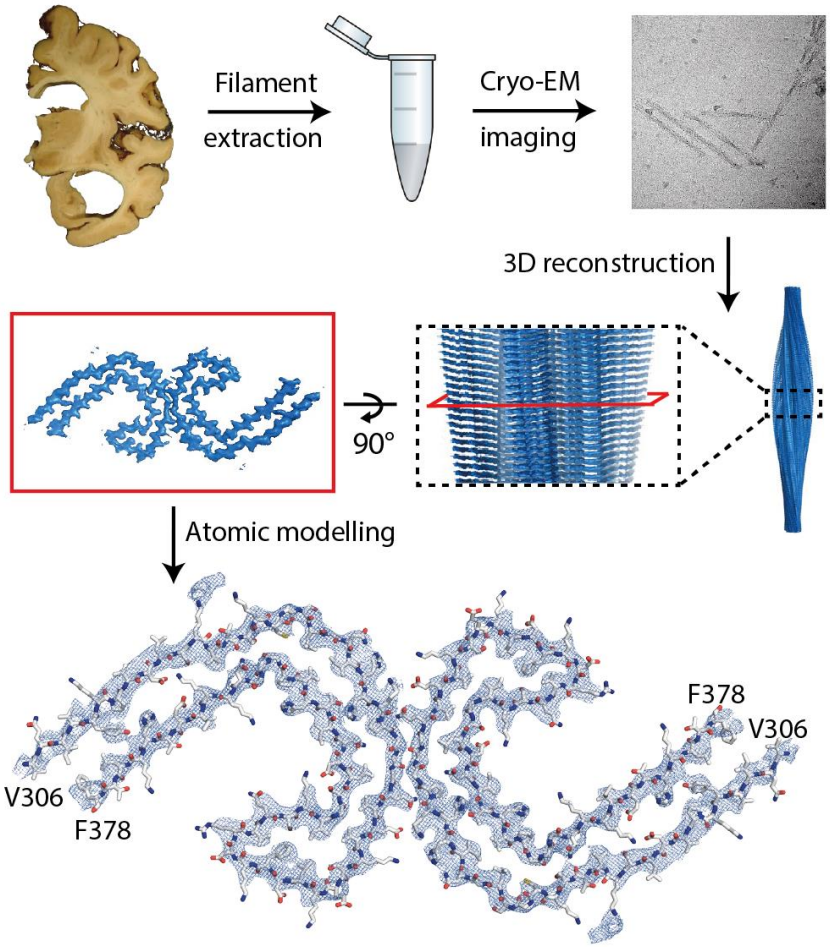


Abnormal Tau Filaments



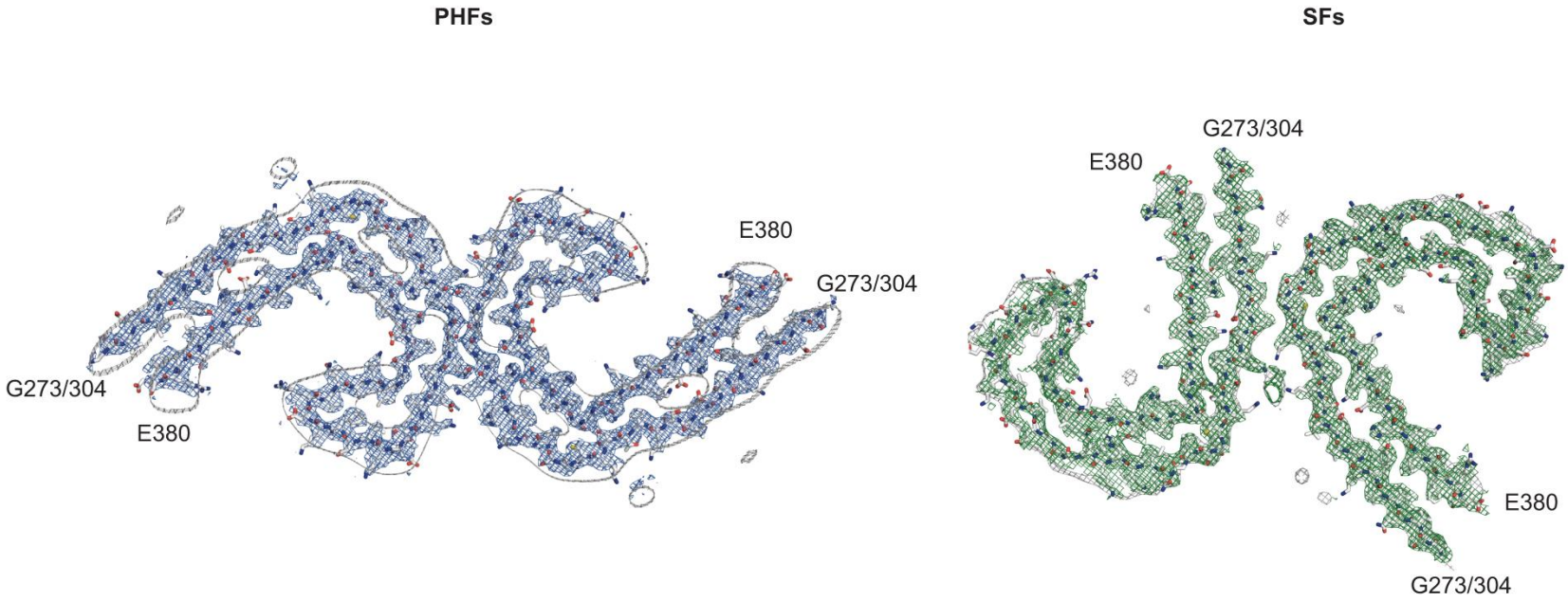
Goedert et al., PNAS 1988
Wischik et al., PNAS 1988a,b

Cryo-EM Structures of Paired Helical Tau Filaments



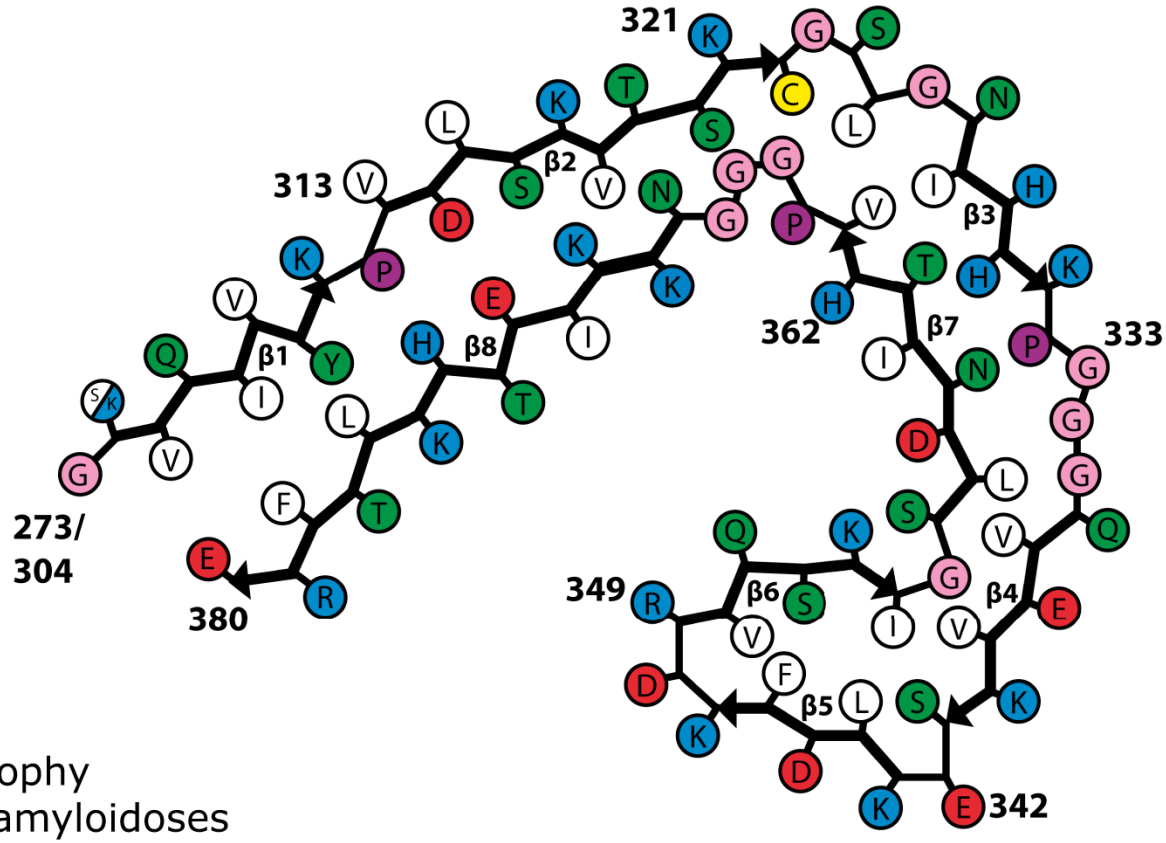
Fitzpatrick et al., Nature 2017

Paired Helical and Straight Filaments

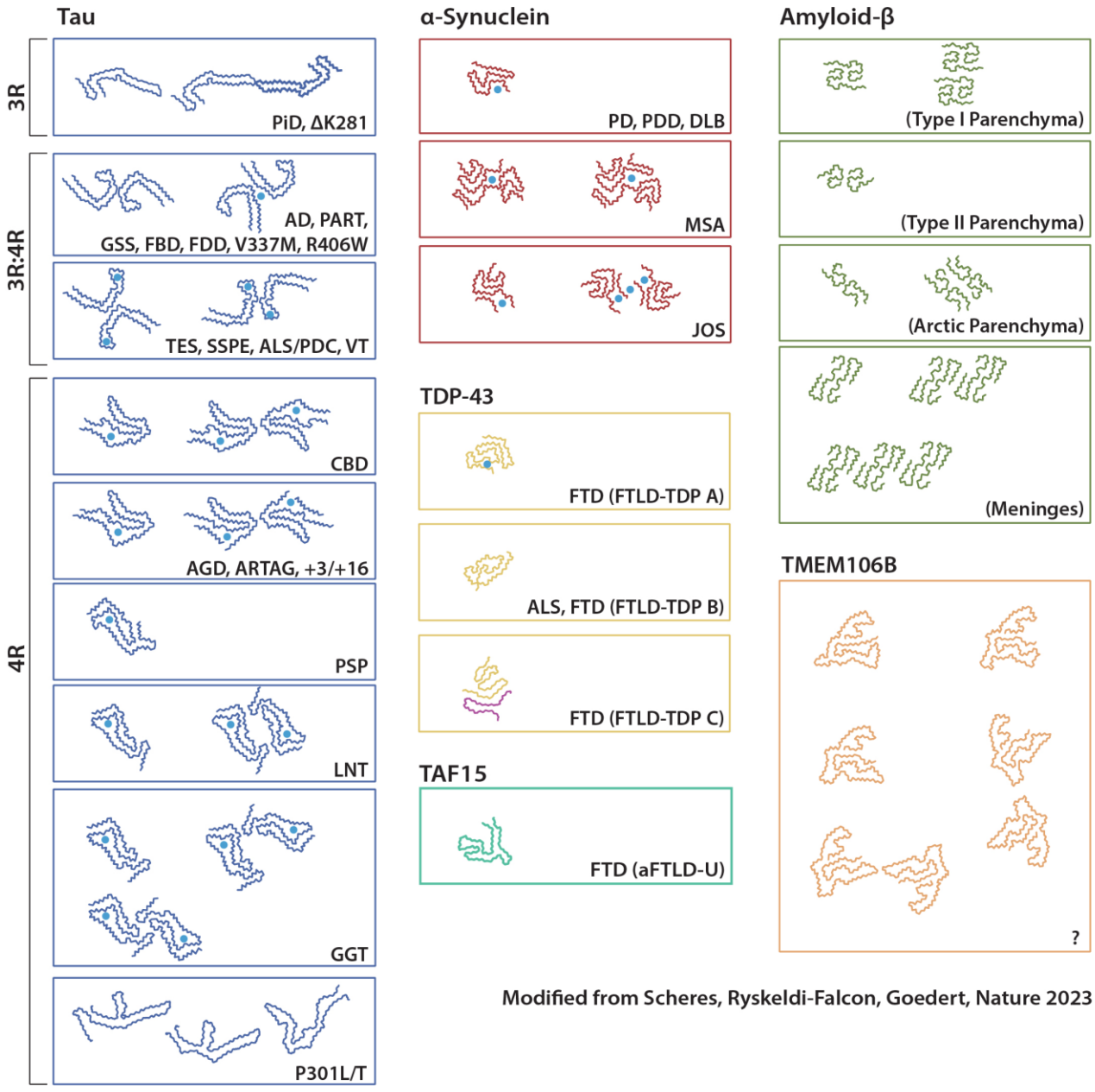


Fitzpatrick et al., Nature 2017
Falcon, Zhang et al., Acta Neuropathologica 2018
Shi et al., Acta Neuropathologica 2021
Hallinan et al., Acta Neuropathologica 2021
Shi, Zhang et al., Nature 2021

Alzheimer Fold



Alzheimer's disease
Posterior cortical atrophy
Some prion protein amyloidoses
Familial British dementia
Familial Danish dementia
Primary age-related tauopathy



Modified from Scheres, Ryskeldi-Falcon, Goedert, Nature 2023

Each sporadic disease with intracellular filamentous amyloid inclusions is characterised by a specific fold, but the same fold can be found in multiple diseases.

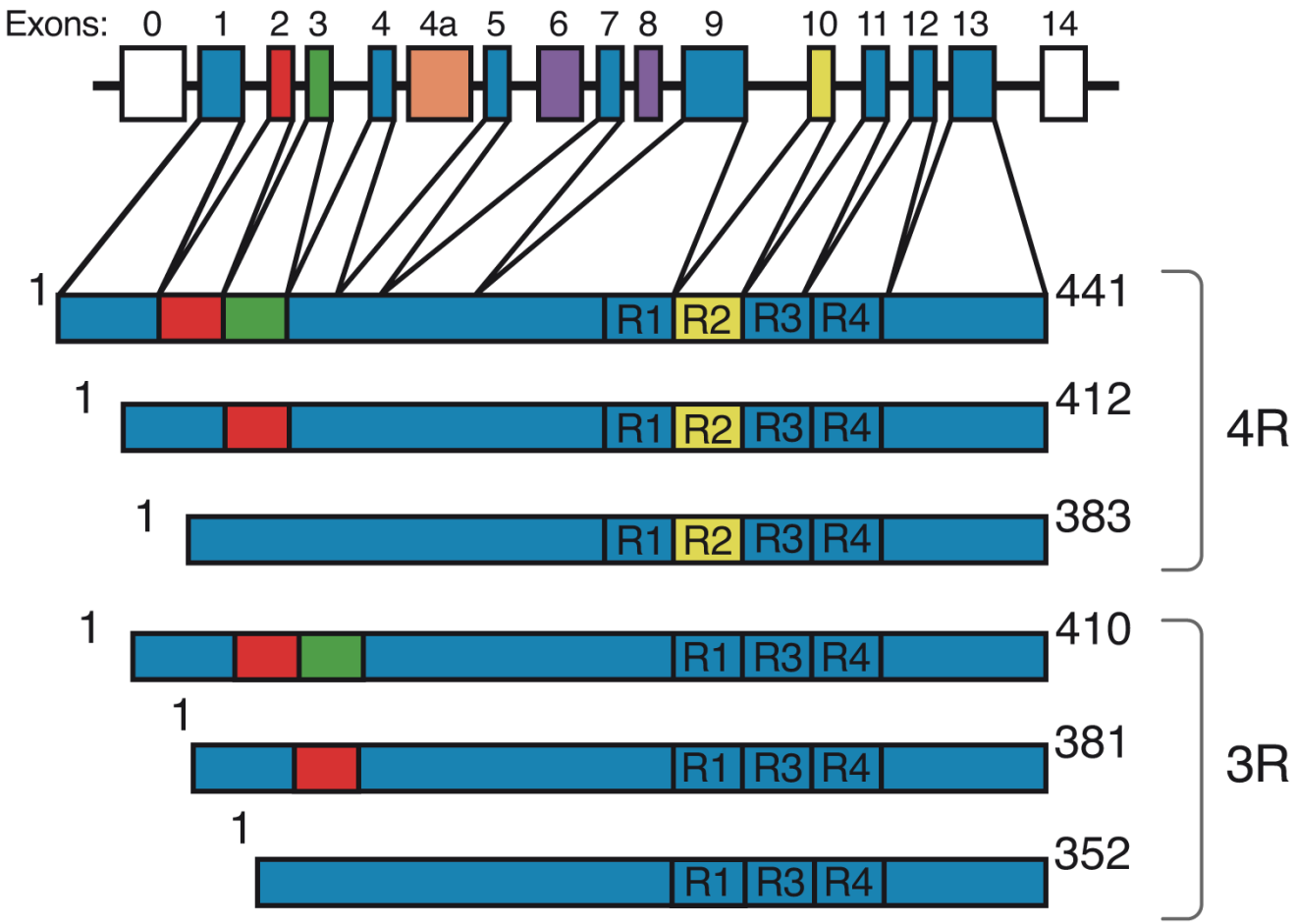
Differences in folds are observed between some diseases, not between individuals with a given disease. Thus, for instance, each case of Alzheimer's disease that we have looked at had the same tau fold.

Where analysed, in a given brain, the same fold is found in different brain regions.

Non-proteinaceous densities of unknown composition are a common finding.

With the possible exception of TMEM106B filaments, the structurally characterised amyloid filaments are made of a structured core and an unstructured fuzzy coat.

Tau Protein



Goedert et al., Neuron 1989

Tauopathies

3R/4R

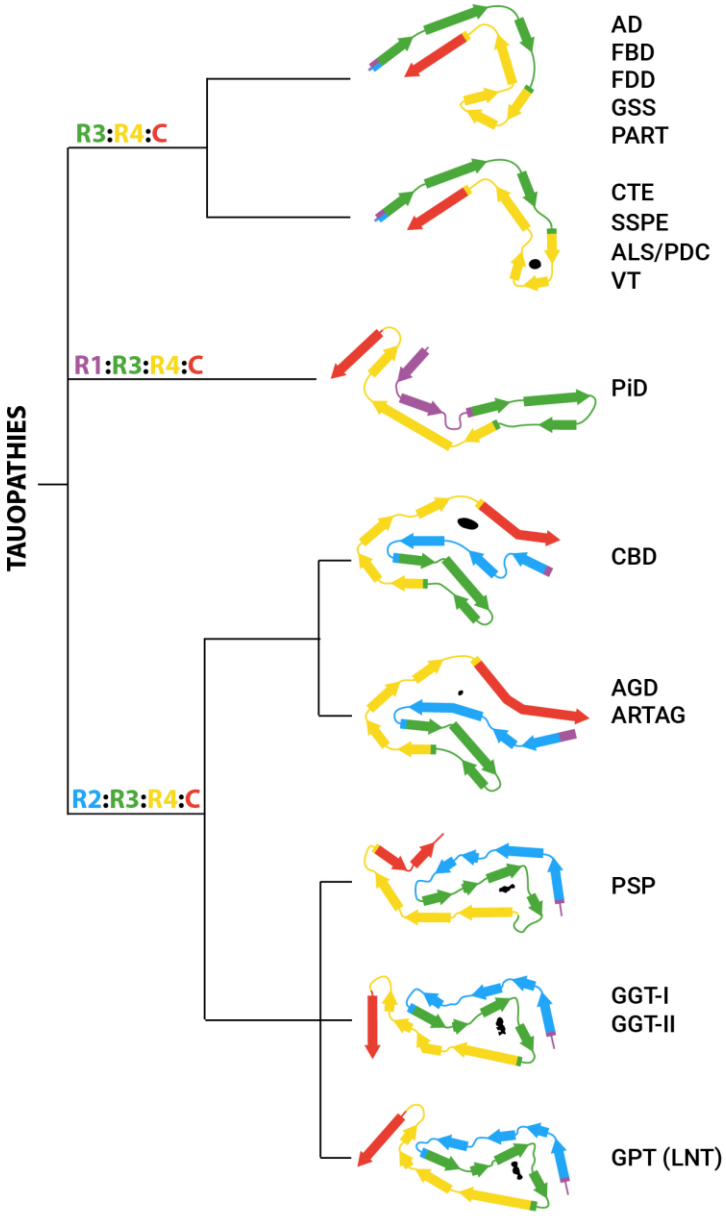
- Alzheimer's disease
- Familial British dementia
- Familial Danish dementia
- Primary age-related tauopathy
- Chronic traumatic encephalopathy

3R

- Pick’s disease

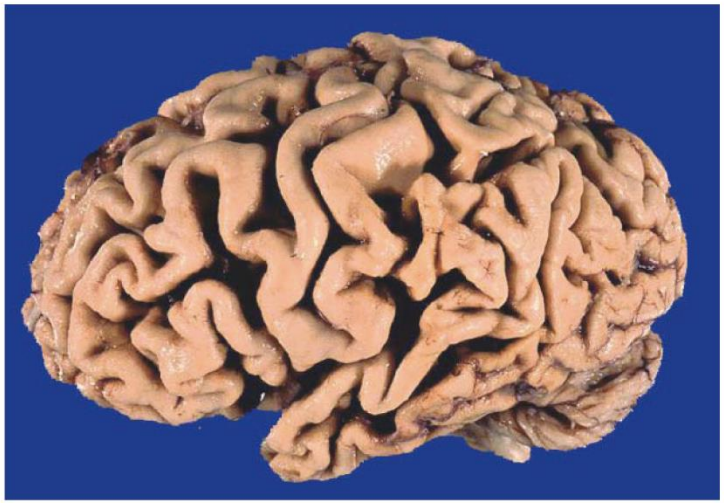
4R

- Corticobasal degeneration
- Argyrophilic grain disease
- Age-related tau astrogliopathy
- Progressive supranuclear palsy
- Globular glial tauopathy

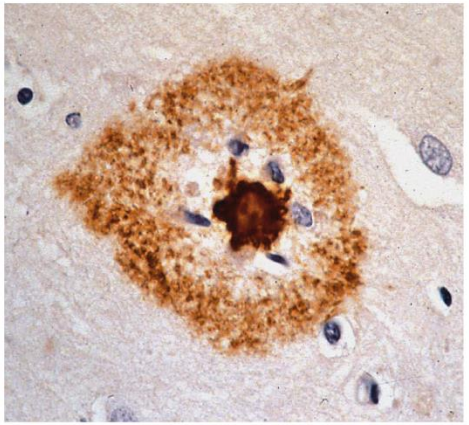


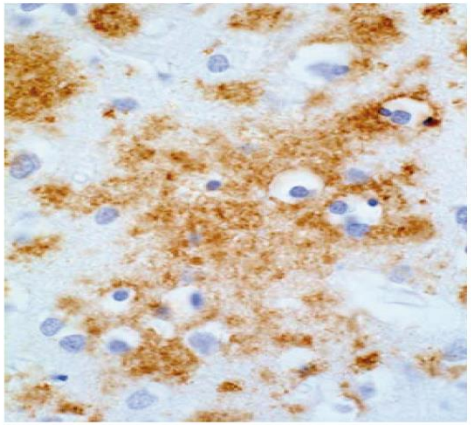
Modified from Shi, Zhang et al., Nature 2021.

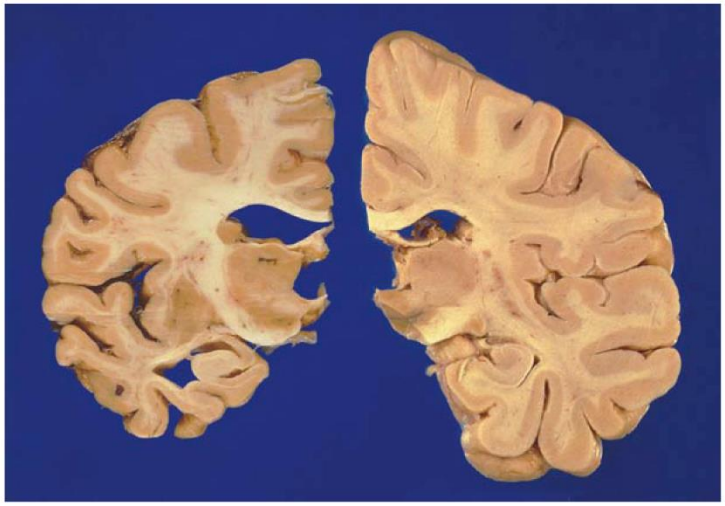
Alzheimer's Disease: Beta-Amyloid and Tau



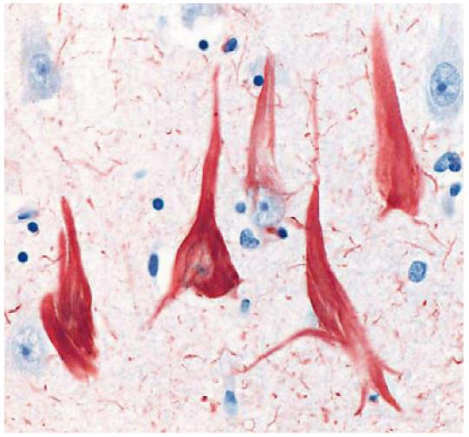
Extracellular deposition of β-amyloid

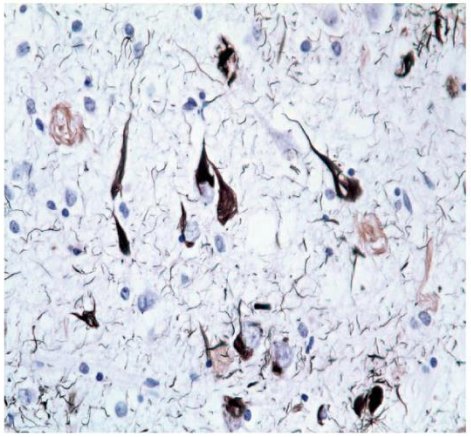




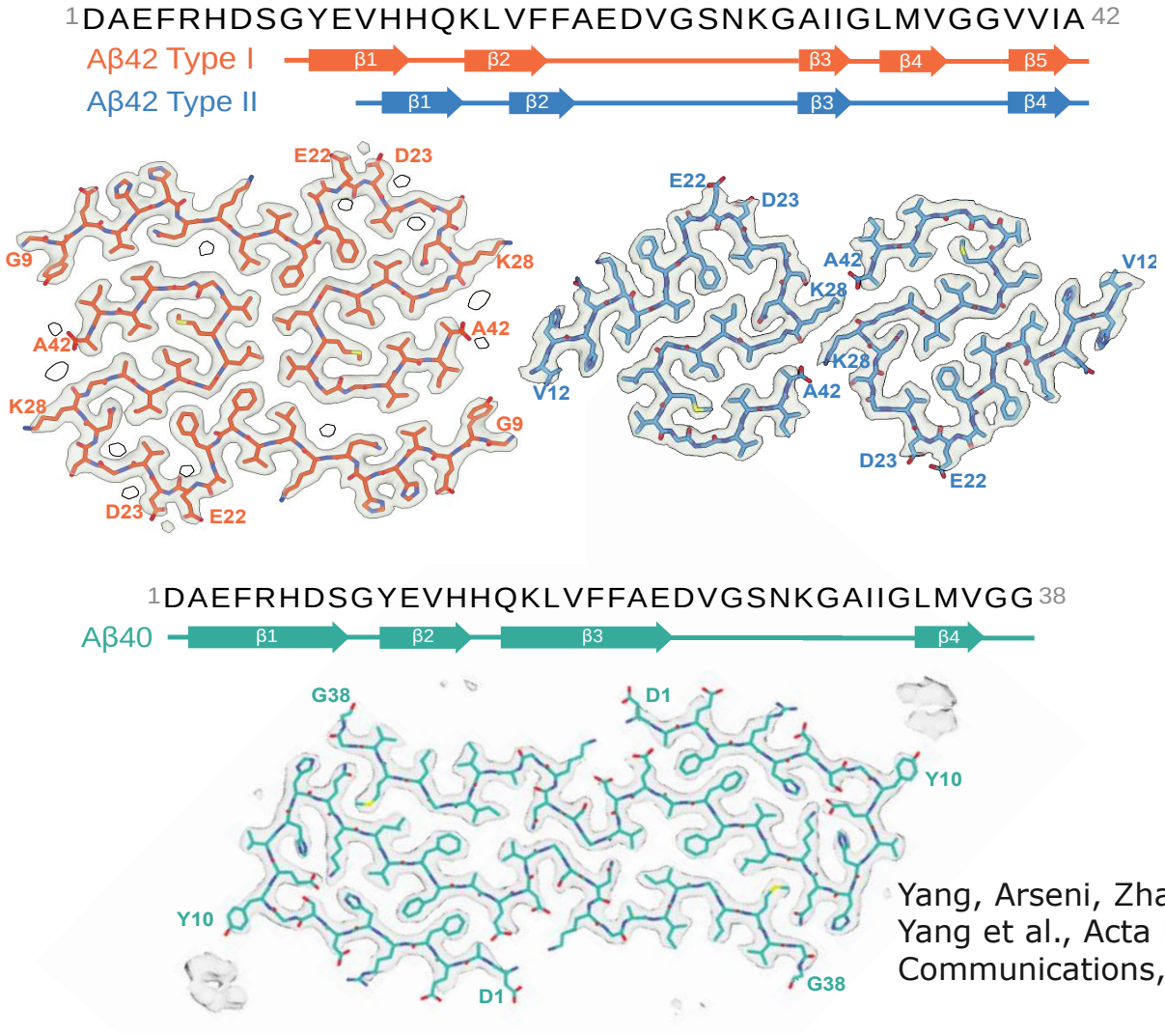


Intracellular assembly of tau protein





Structures of Amyloid-beta Filaments from Human Brains



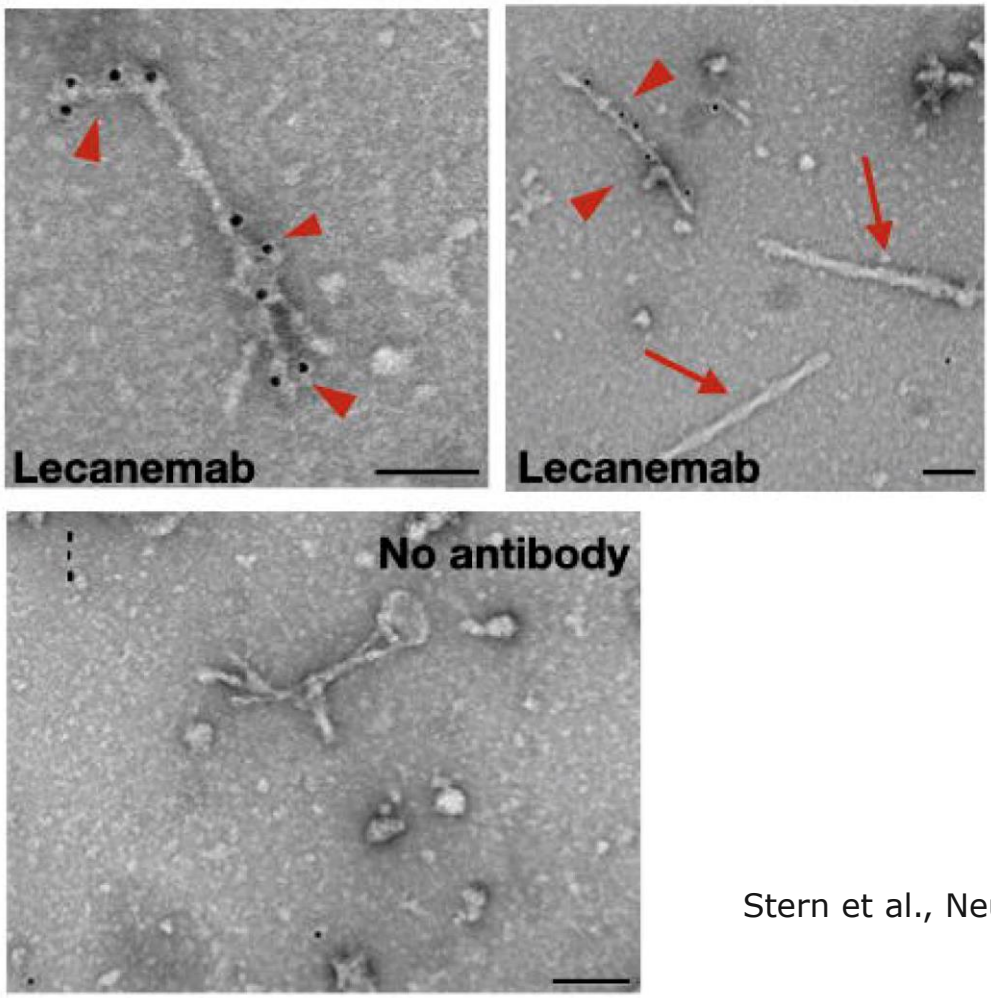
Yang, Arseni, Zhang et al., Science 2022
Yang et al., Acta Neuropathologica Communications, 2023

Diffusible, highly bioactive oligomers represent a critical minority of soluble Aβ in Alzheimer's disease brain

Wei Hong[1] · Zemin Wang[1] · Wen Liu[1] · Tiernan T. O'Malley[1] · Ming Jin[1] · Michael Willem[2] · Christian Haass[2,3,4] · Matthew P. Frosch[5] · Dominic M. Walsh[1]

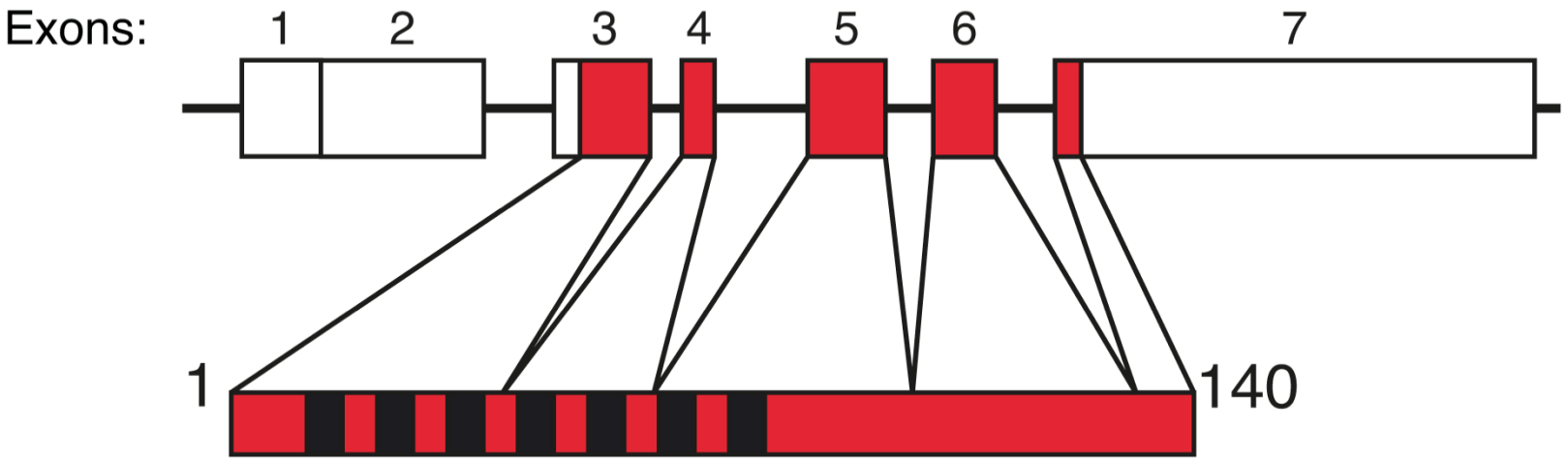
Acta Neuropathologica 2018

Antibody Lecanemab binds to Amyloid-β 42 Filaments from Brain



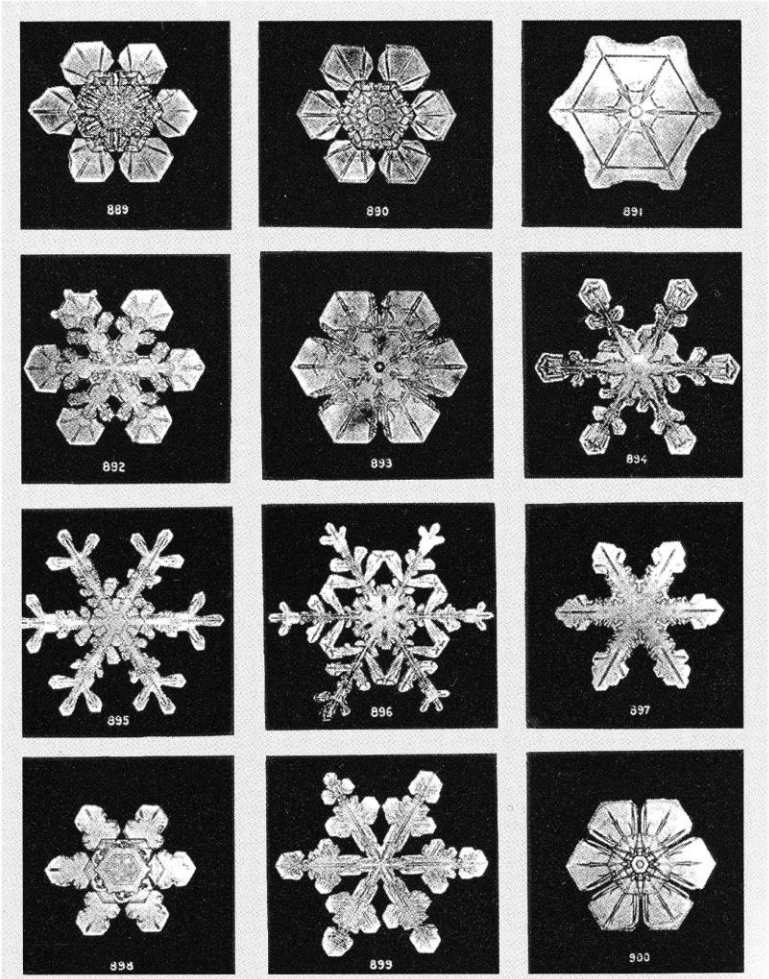
Stern et al., Neuron 2023

α-Synuclein



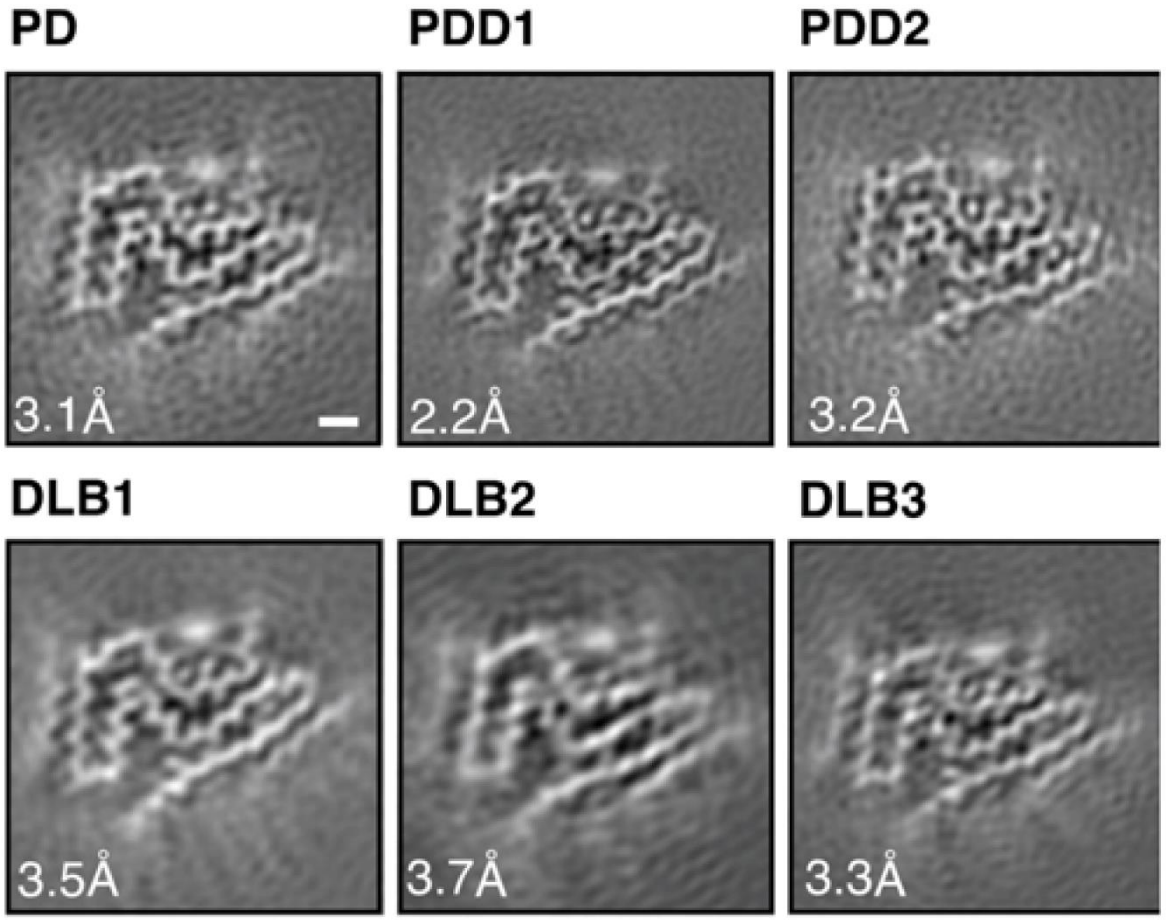
Distinct Molecular Conformers (Protein Strains)?

α-Synuclein Assemblies
Lewy Body Diseases
Multiple System Atrophy



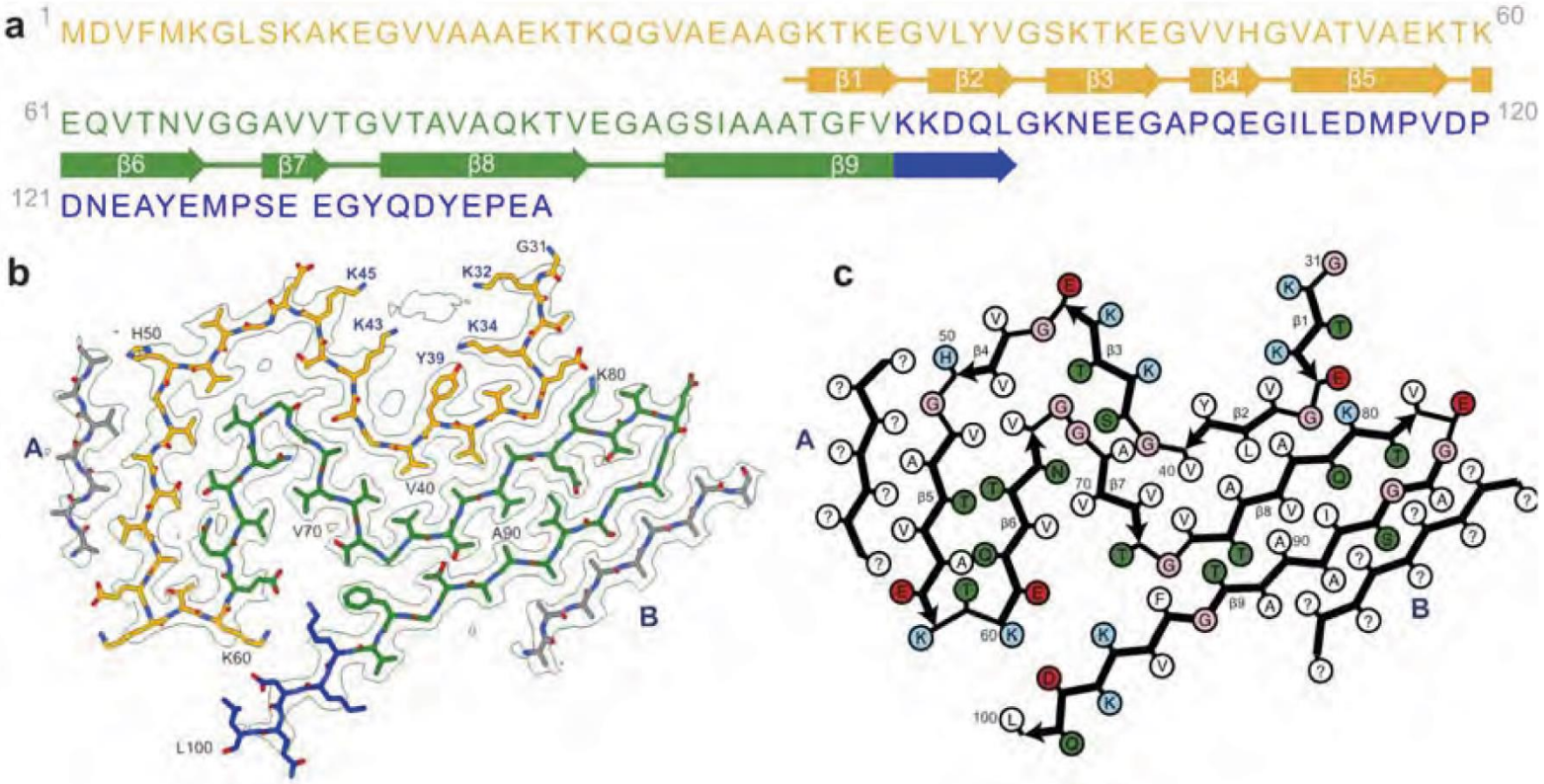
Snowflake crystals by Wilson Bentley, c. 1902

Cross-Sections of α-Synuclein Filaments



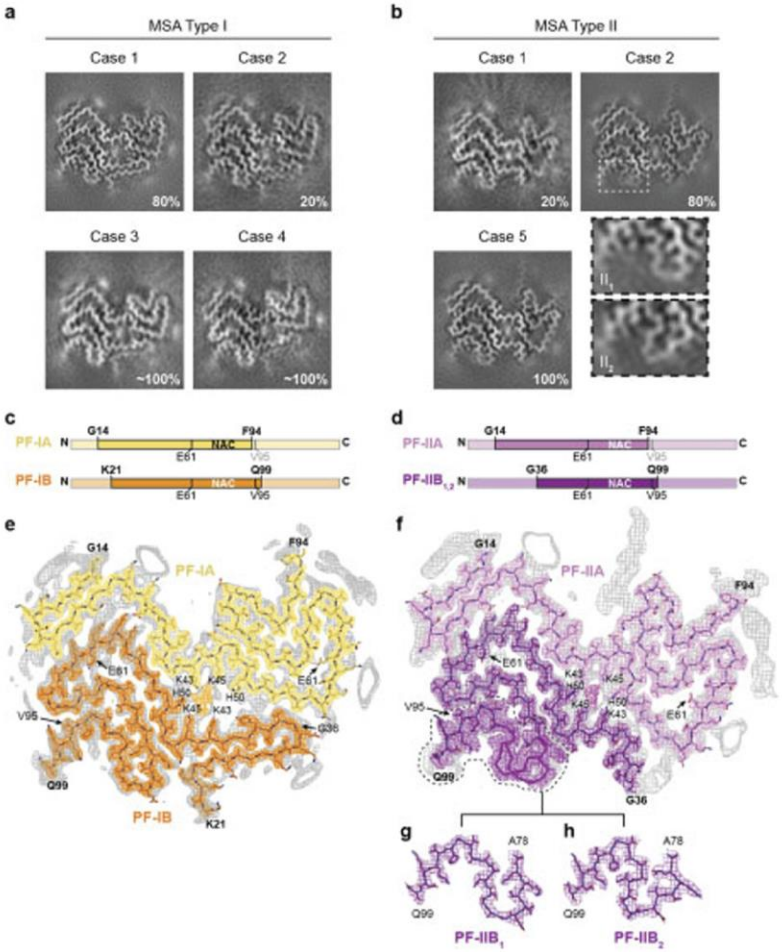
Yang et al., Nature 2022

Lewy Fold



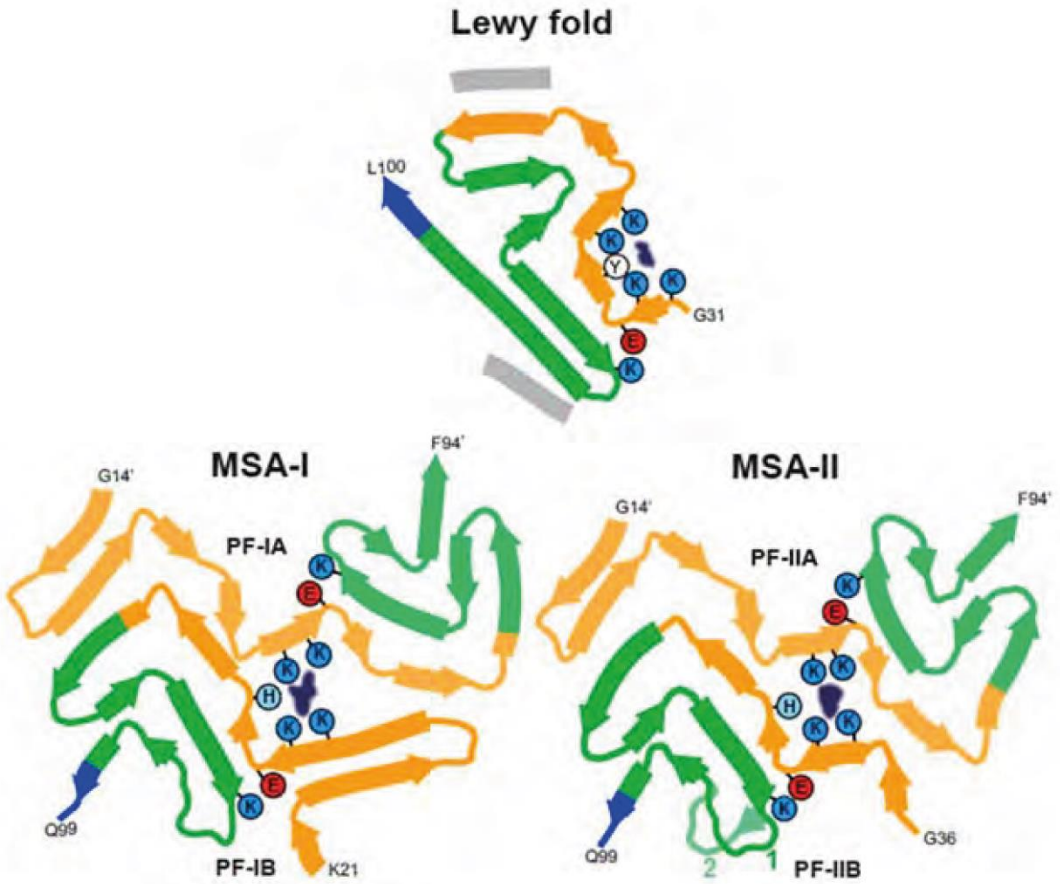
Yang et al., Nature 2022

Type I and Type II α-Synuclein Filaments from MSA Brain



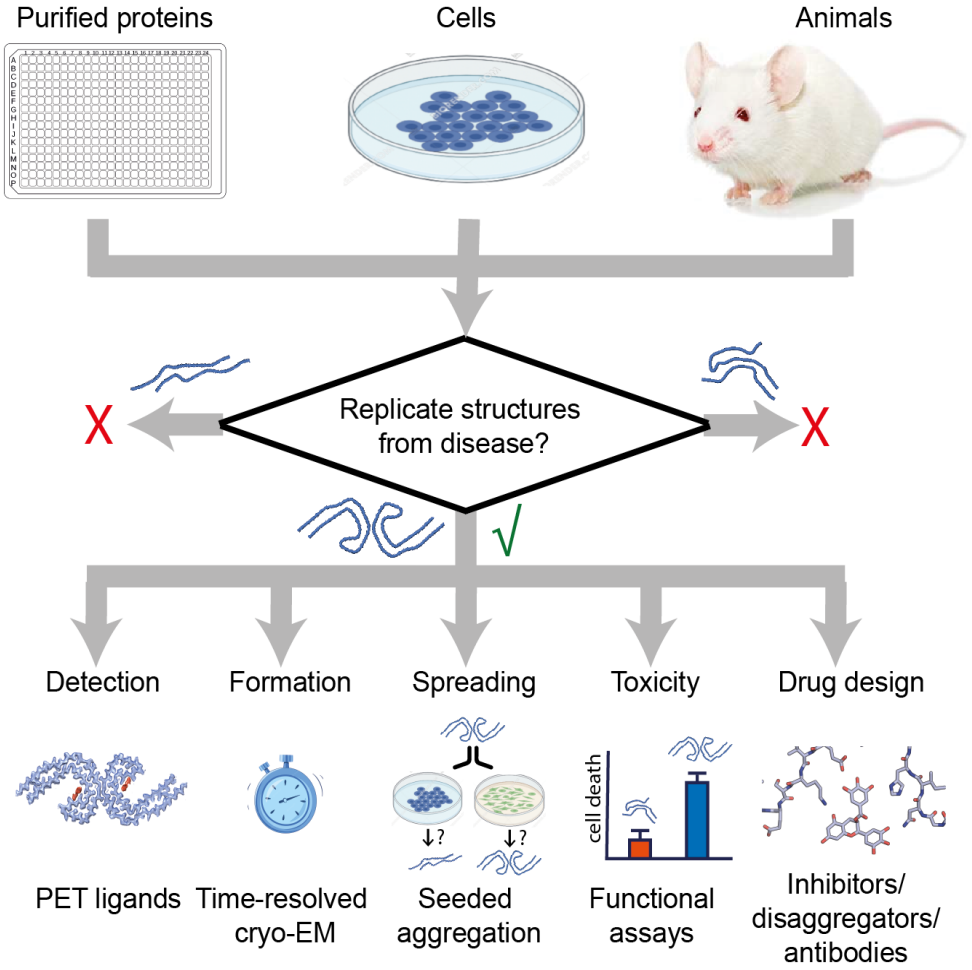
Schweighauser, Shi et al., Nature 2020

Lewy Fold and MSA Folds

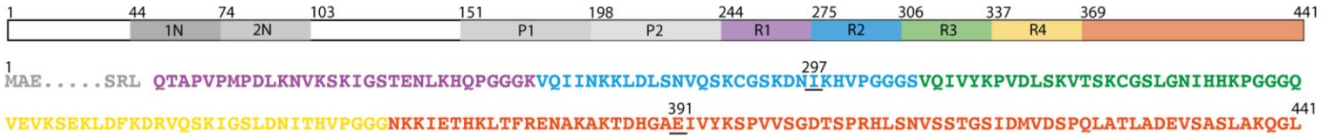


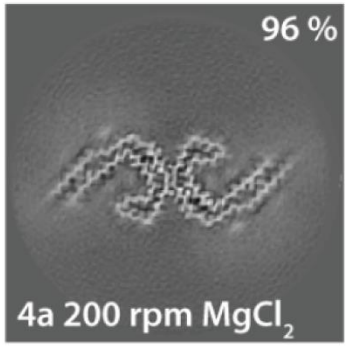
Impact of Amyloid Structures

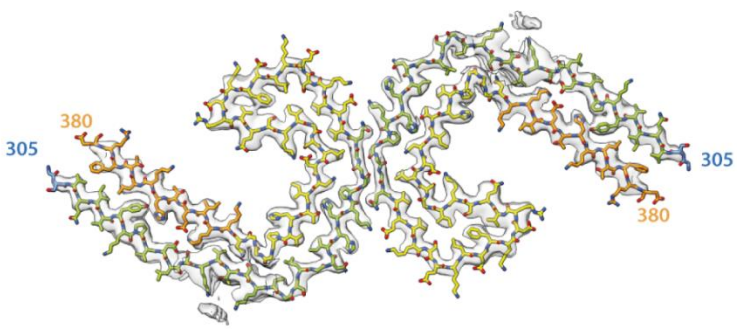
Scheres, Ryskeldi-Falcon, Goedert, Nature 2023

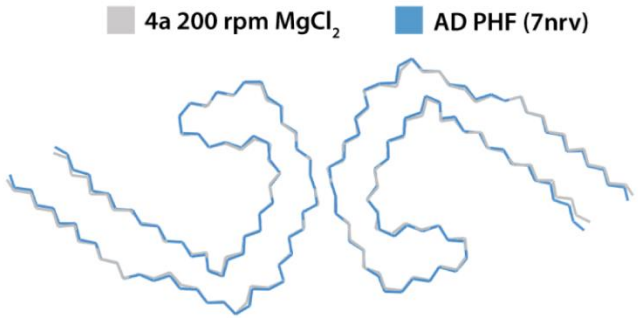


Assembly of Recombinant Tau (297-391) into Filaments identical to AD PHFs



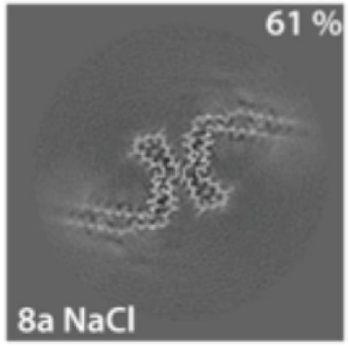


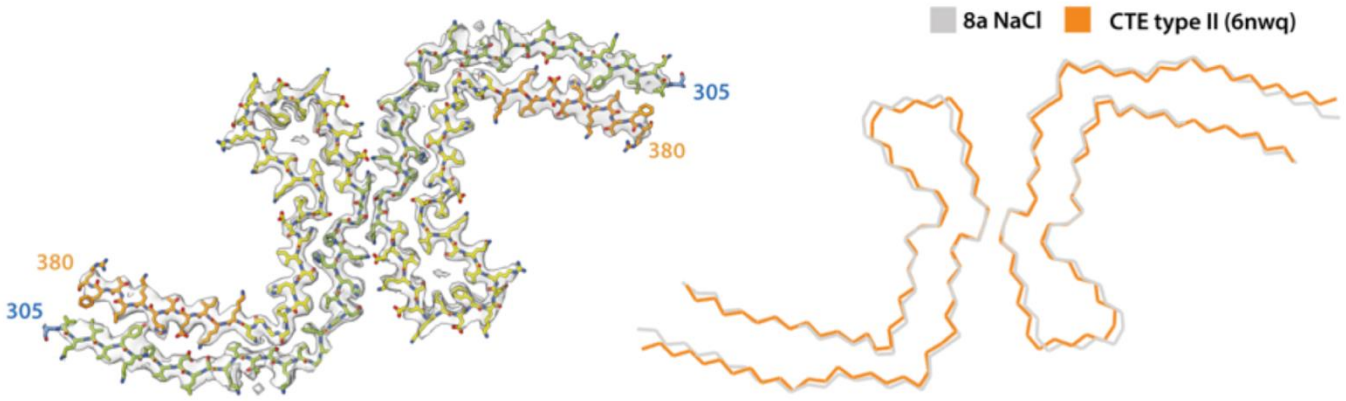




Lövestam et al., eLife 2022

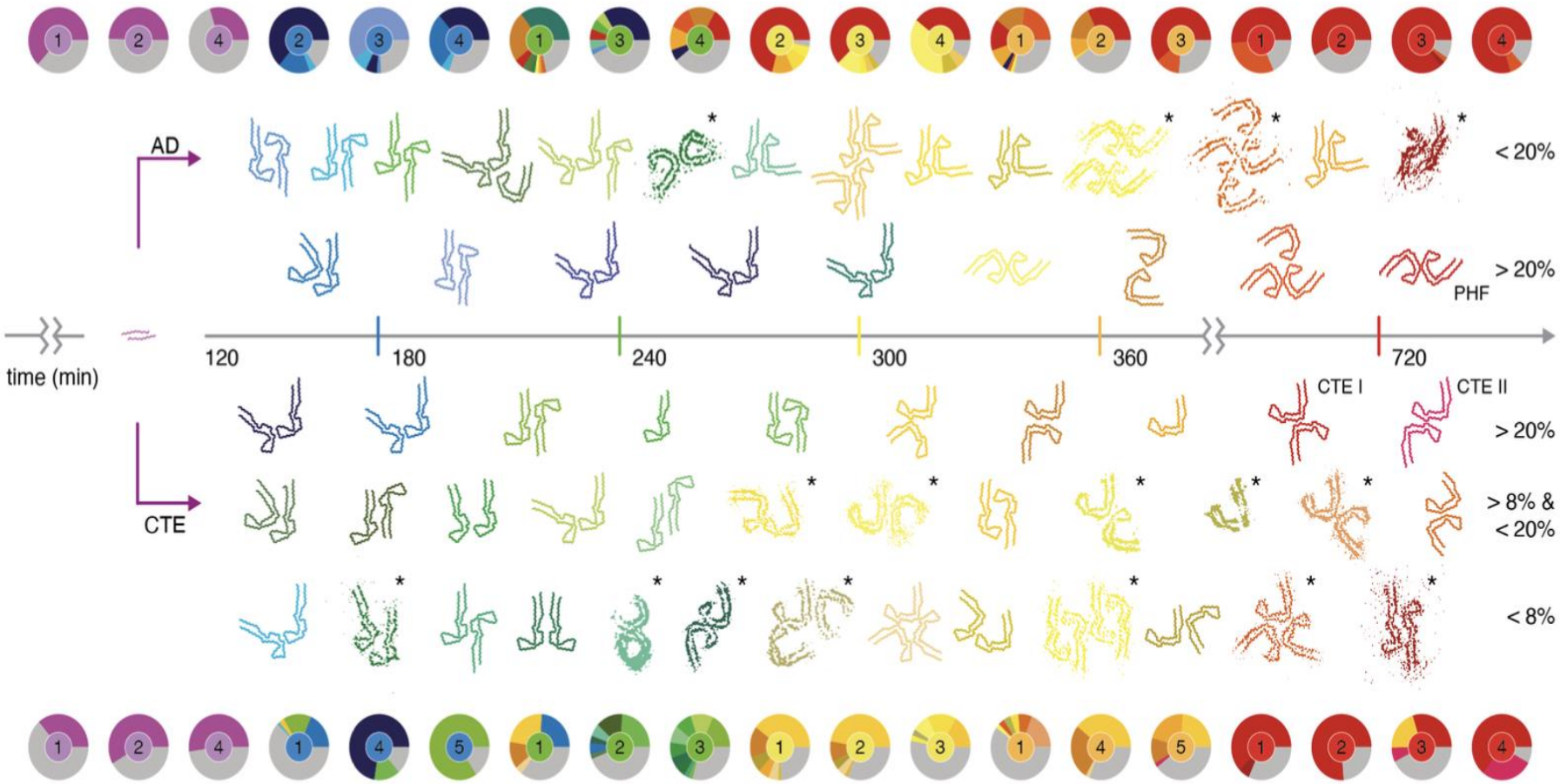
Assembly of Recombinant Tau (297-391) into Filaments identical to CTE Type II Filaments





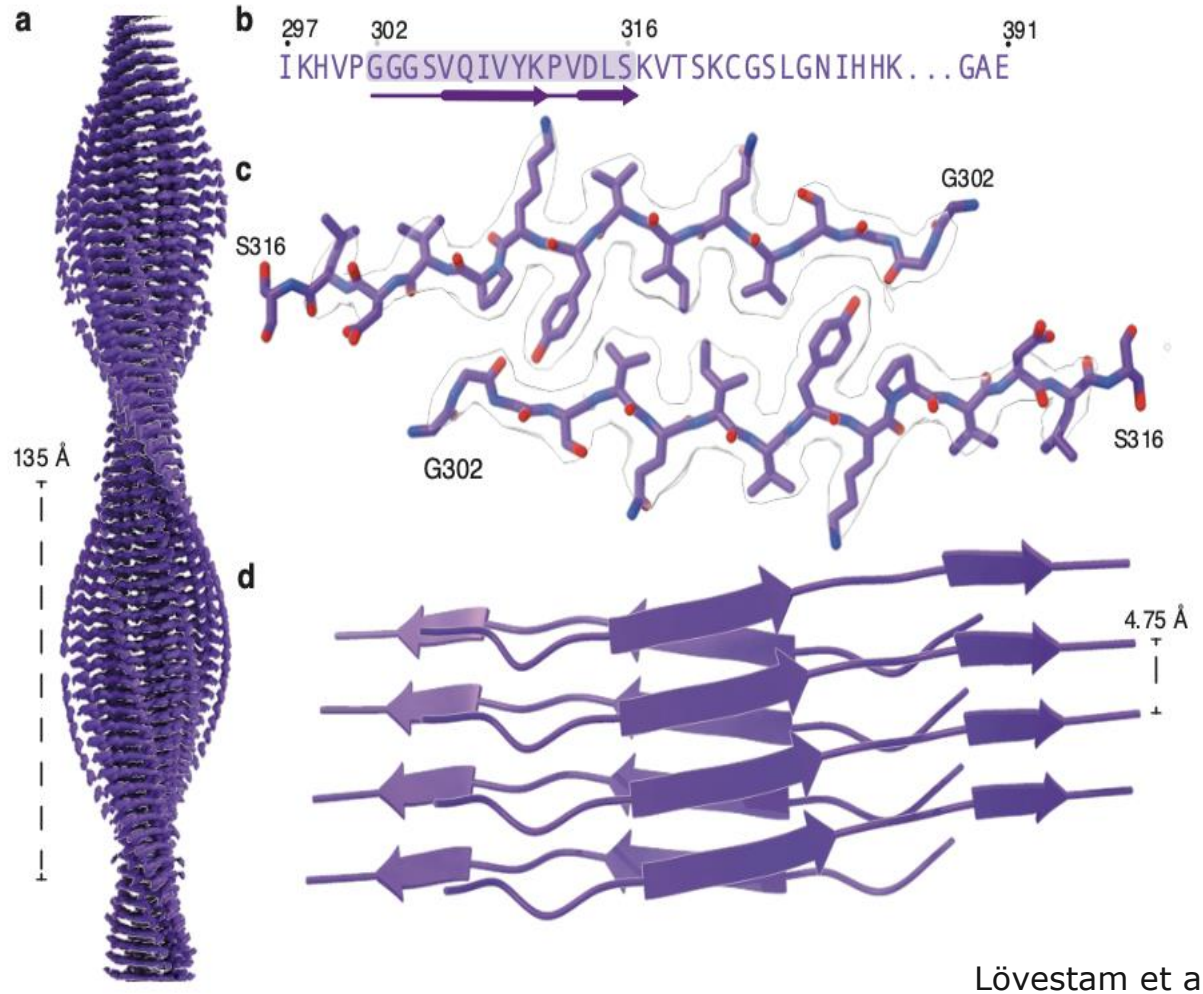
Lövestam et al., eLife 2022

Structures in the Assembly Reactions



Lövestam et al., Nature 2024

Structure of the FIA



Lövestam et al., Nature 2024

Tau Proteins of Alzheimer Paired Helical Filaments: Abnormal Phosphorylation of All Six Brain Isoforms

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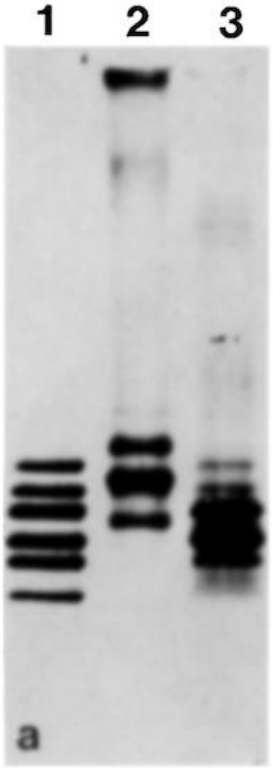
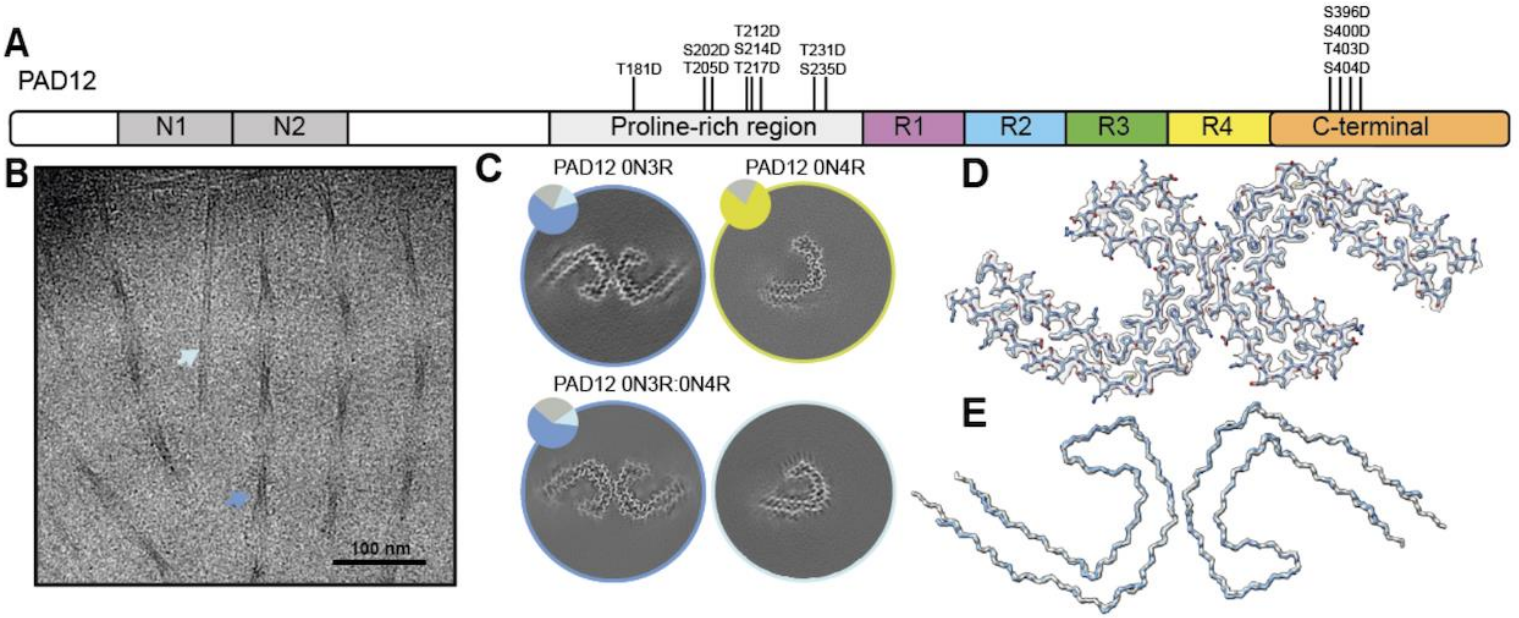


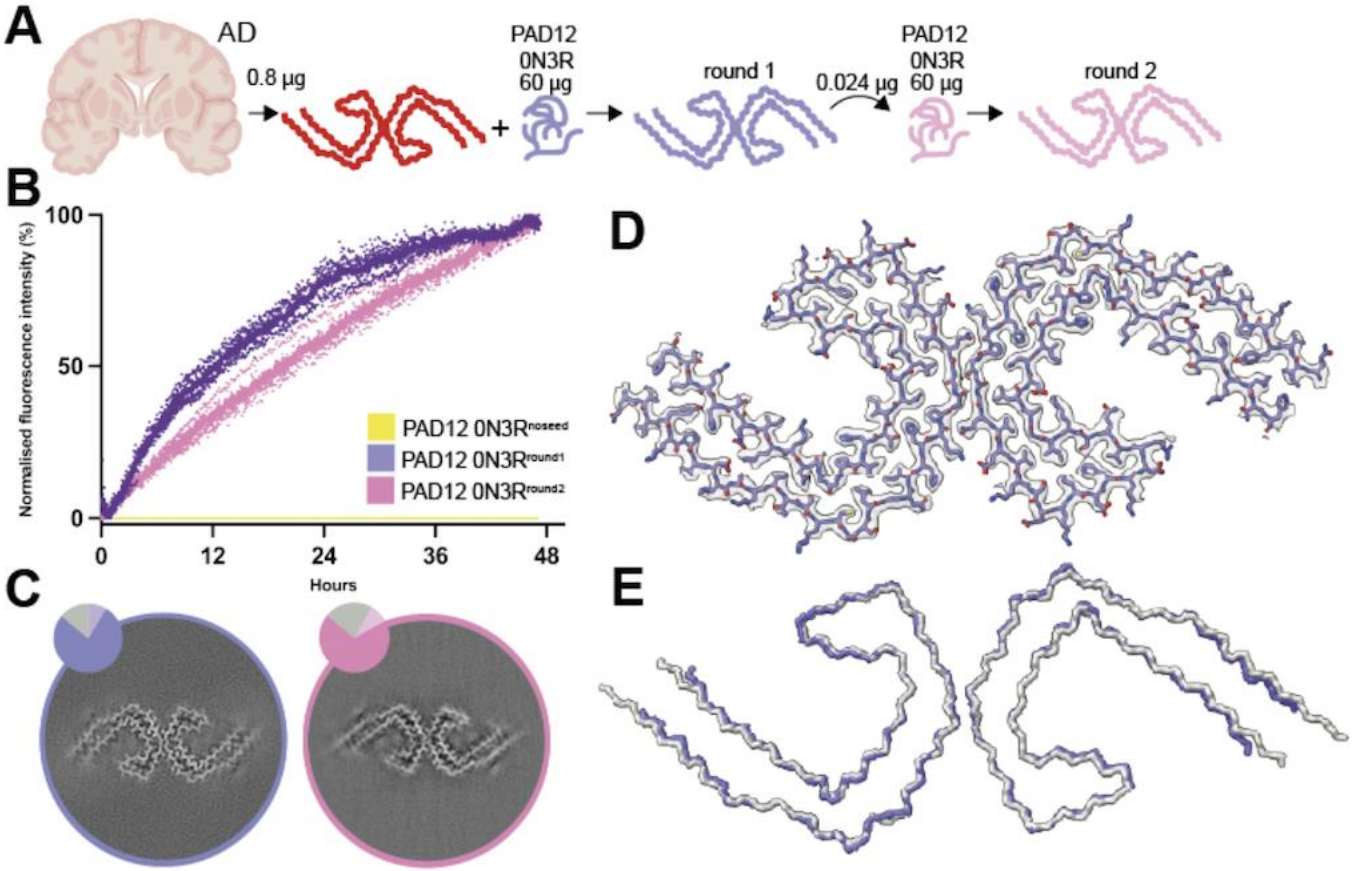
Neuron 1992

Cryo-EM Analysis of PAD12 Tau Filaments



Lövestam et al., submitted (bioRxiv 2024)

Multiple Rounds of *In Vitro* Seeded Assembly



Lövestam et al., submitted (bioRxiv 2024)

Our perspective…

- The same protein can adopt many different amyloid folds
  - Yet structures are the same within each brain/disease
  - Highly specific processes in each disease?
  - Amyloid structure provides a ***neuropathological description at the atomic level***
  - And thereby a ***handle to study disease***

- Two scenarios:
  - Distinct structures affect disease processes differently
  - Structure doesn't matter for disease; it is merely a reflection of where they form

- What drives the formation of specific folds in disease?
  - Cofactors/PTMs/cellular environment/other?
  - Study using in vitro assembly, cellular models & animals

- Your favourite model may not be relevant for disease…
  - ***We need better model systems to study this!***

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