Emerging Neurodegenerative Biomarkers

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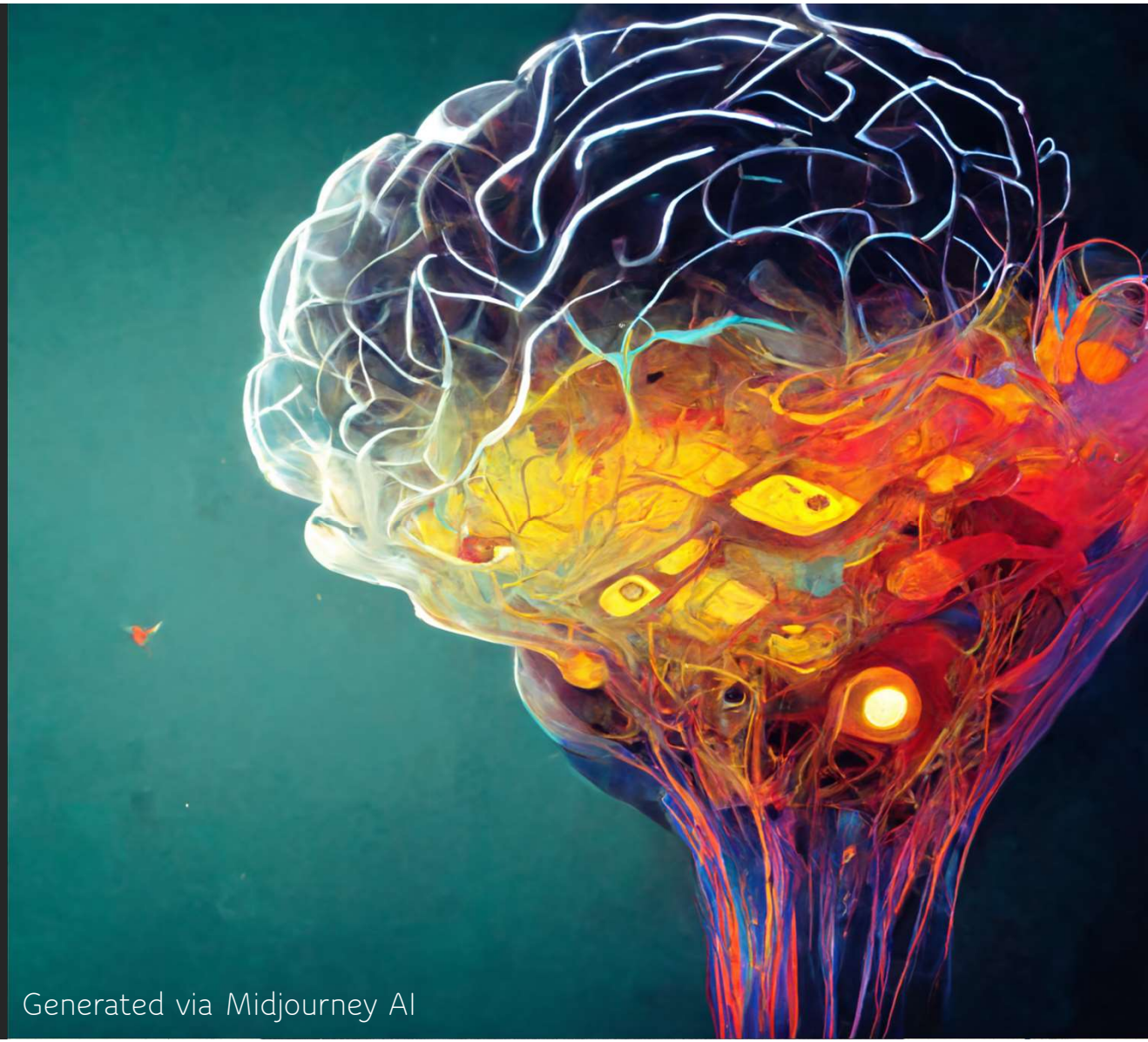
Assistant Professor
Ochsner Neurocognitive Program



Presenter Disclosure

I have no current or past relationships with commercial entities.

Potential for conflict(s) of interest: None

Commercial Support Disclosure

To the presenter knowledge, this program has received no financial or in-kind support from any commercial or other organization.

Potential for conflict(s) of interest: None

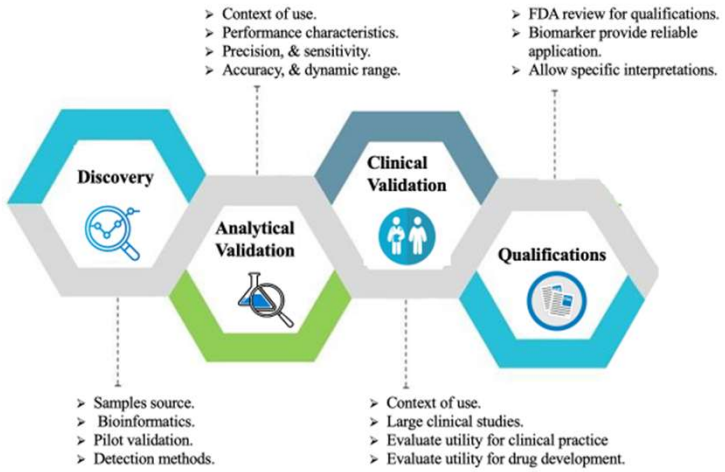
Development of Neurodegenerative Biomarkers

Neurodegenerative diseases are a heterogeneous group of disorders that are characterized by the progressive degeneration of the structure and function of the CNS and/or PNS.

Biomarkers for neurodegenerative diseases may allow

- Early Diagnosis
- Disease staging
- Disease Monitoring
- Disease Prognostication
- Therapeutic Intervention

Biomarker development occurs in consecutive phases and begins with discovery



Beach et al., 2013; Rizzo et al., 2018

Development of Neurodegenerative Biomarkers
Bioinformatics/International Biobanks

Virginia M.-Y. Lee, PhD

John Q. Trojanowski, MD. PhD

1991

UPenn Center for Neurodegenerative Disease Research (CNDR)

- First National NIH-funded ADCC

2004

Alzheimer's Disease Neuroimaging Initiative (ADNI)-1/GO/2/3

2008

UCSF Neurodegenerative Disease Brain Bank

2009

Mayo Clinic Biobank

2010

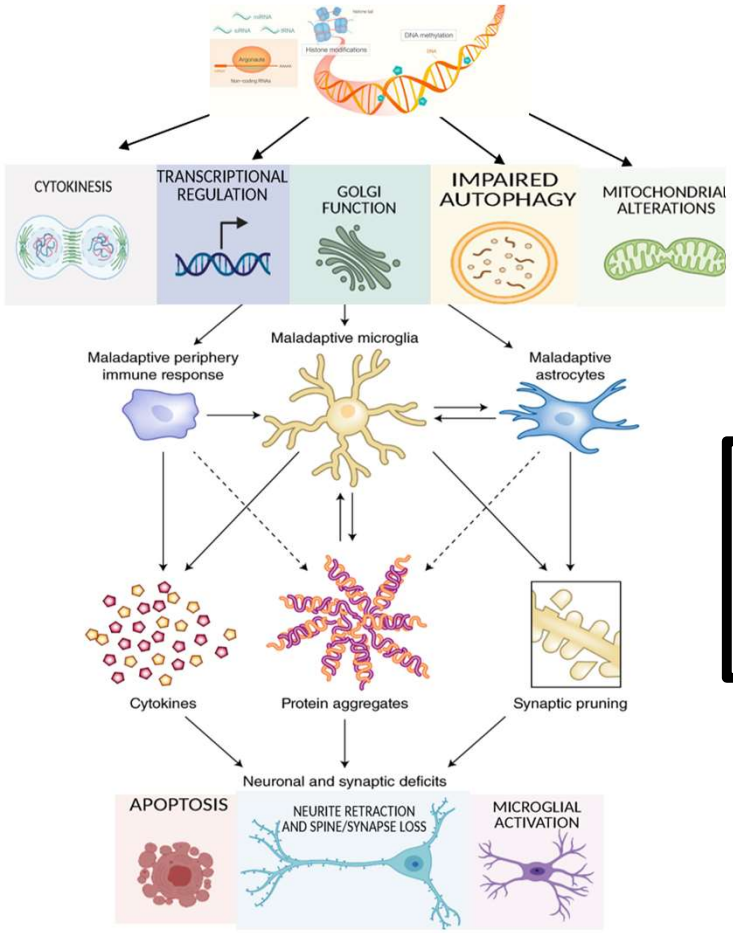
Swedish BioFINDER Study 1/2

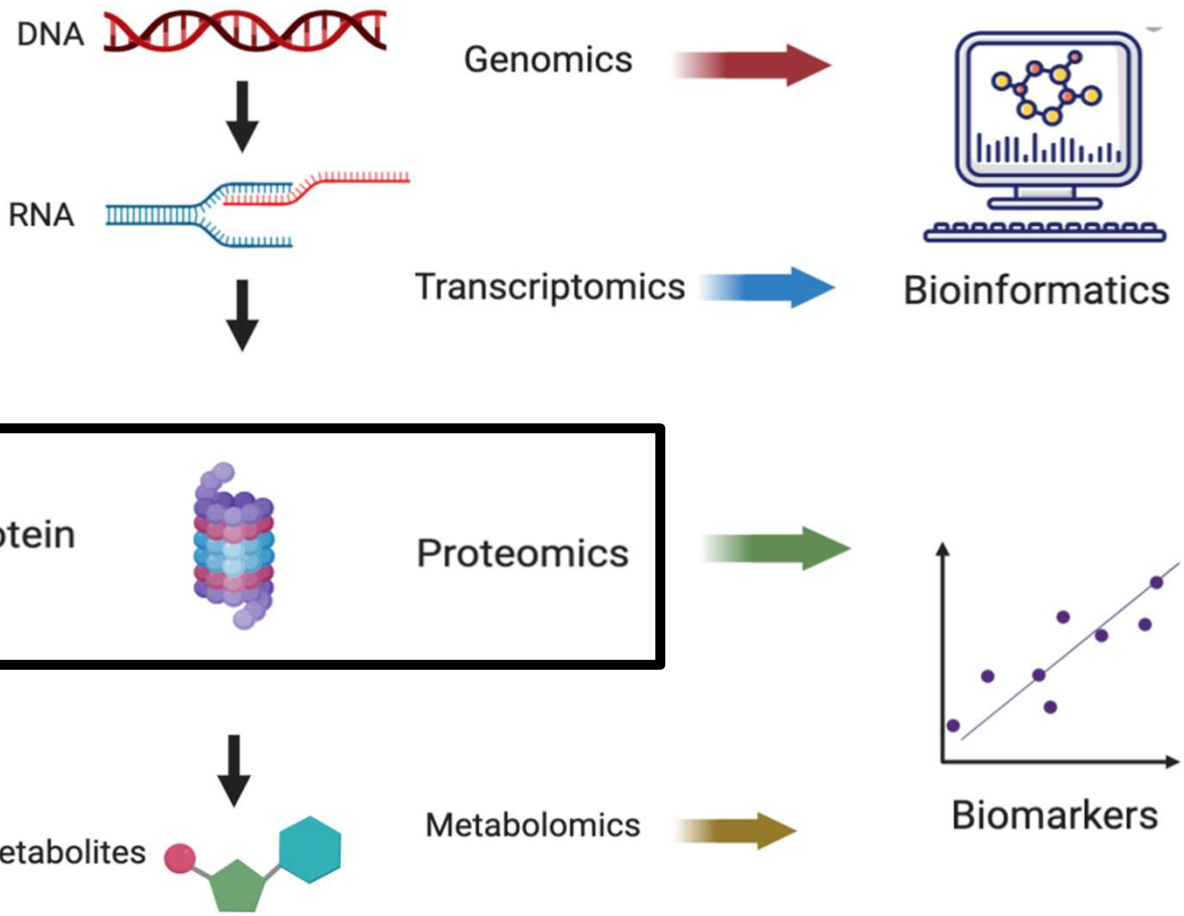
2015

Joint Programme – Neurodegenerative Disease Research (JPND)

Rosengren et al., 1996; Giannella et al., 2021; Waury et al., 2022

Where to begin?





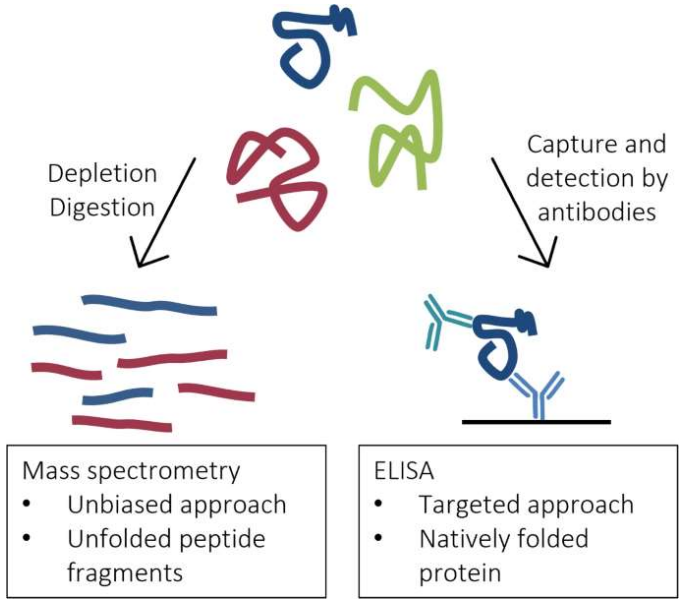
Development of Neurodegenerative Biomarkers
Bioinformatics

First-generation – Immunoblot

Second-generation - Enzyme-linked immunosorbent assay (ELISA)

Third-generation - Electrochemiluminescence (ECL)

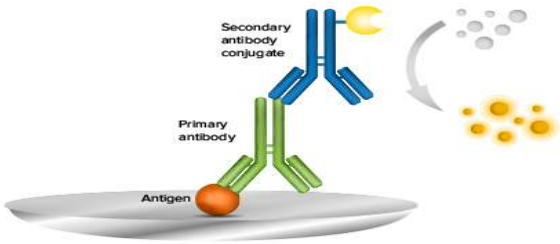
Fourth-generation – Ultrasensitive array (Simoa, PEA, SMC, IMR, IP/MS, LC/MS/MS)



Rosengren et al., 1996; Khalil et al., 2018; Waury et al., 2022

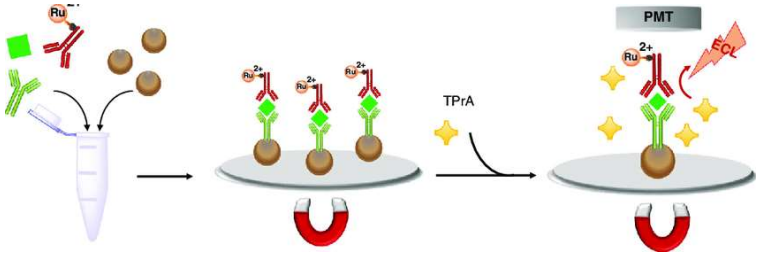
2ND

Enzyme-linked immunosorbent assay (ELISA)



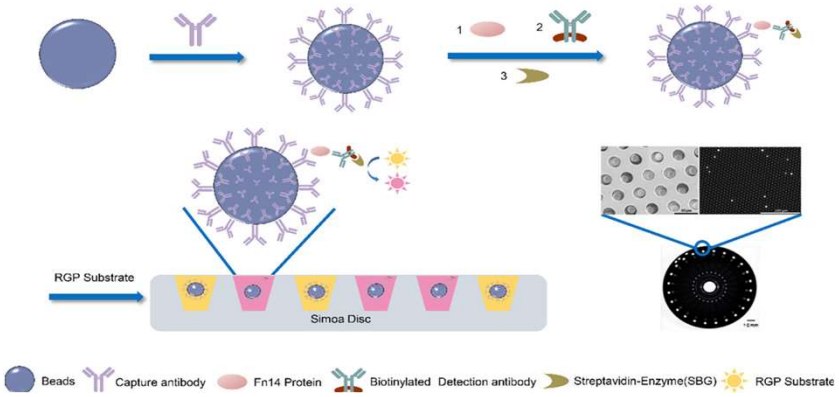
3RD

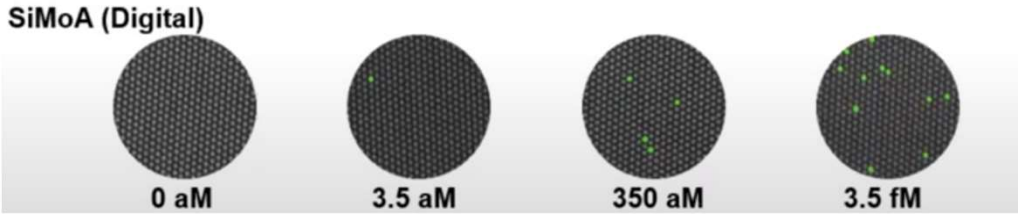
Electrochemiluminescence (ECL) immunoassay



4TH

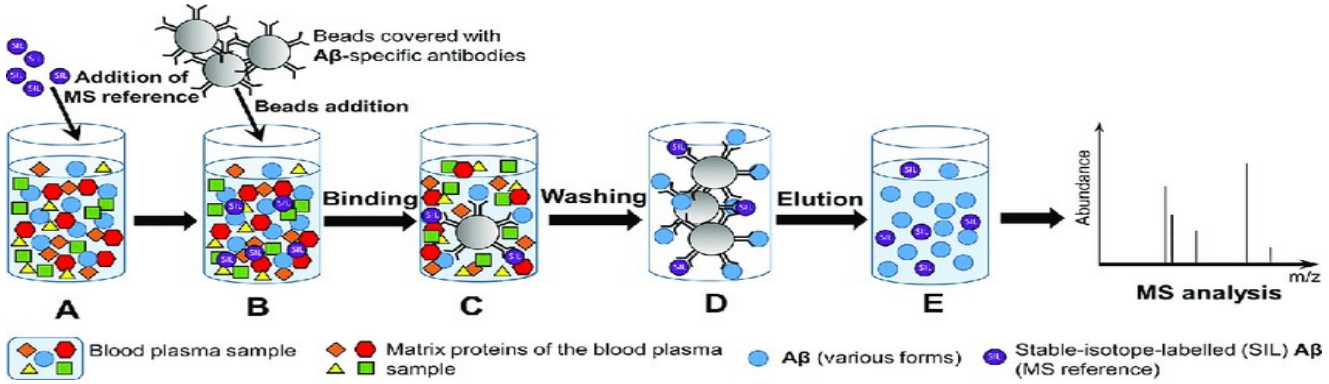
Single Molecule Counting (SMC/Simoa)





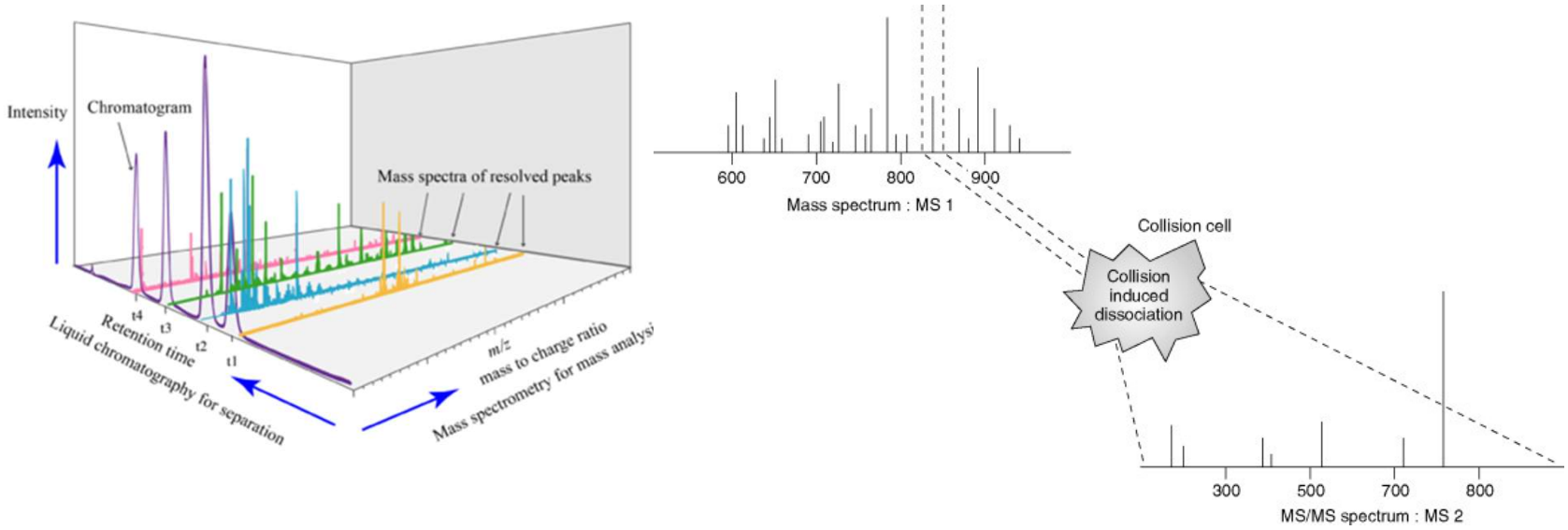
4TH

Immunoprecipitation Mass Spectrometry (IP/MS)

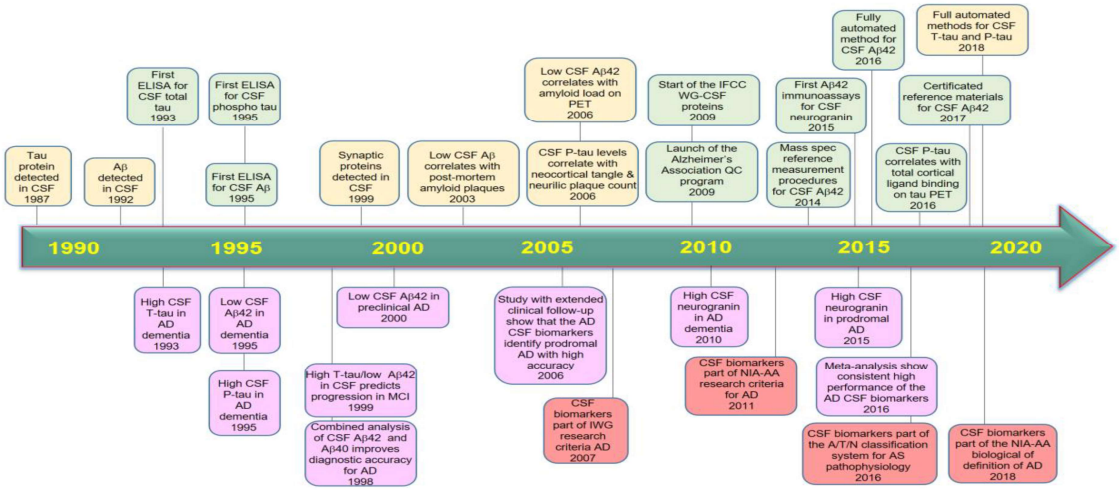


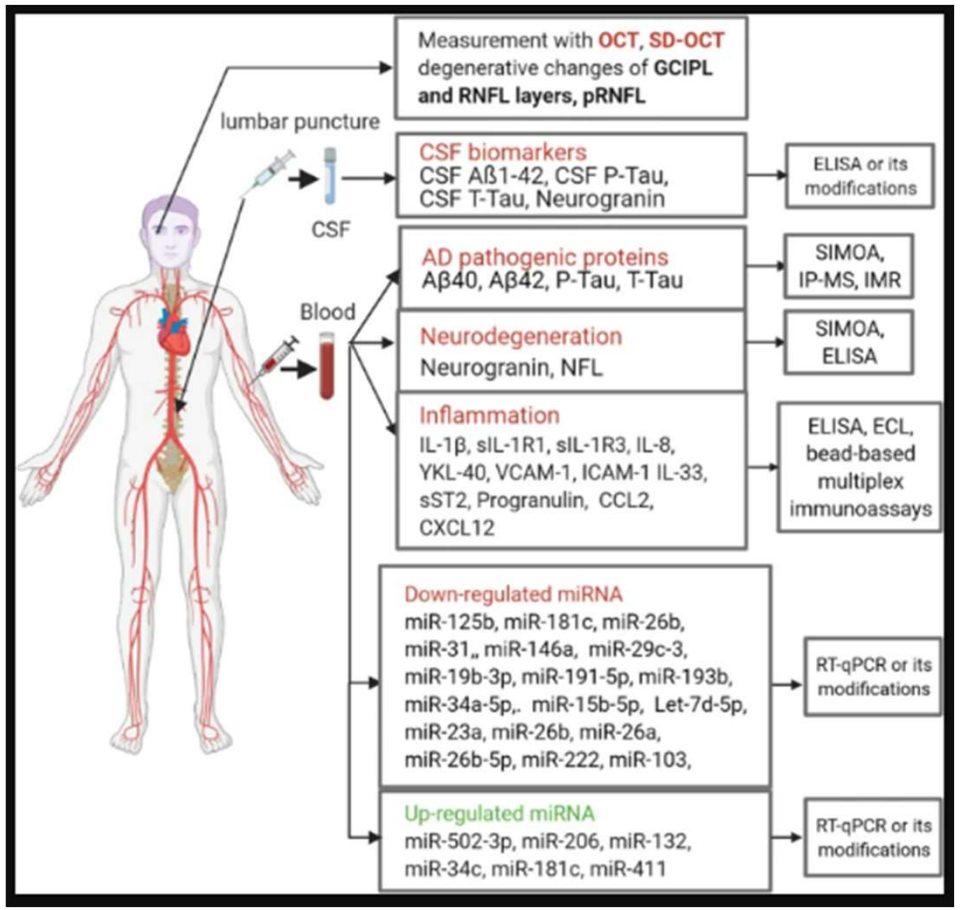
4TH

Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS)

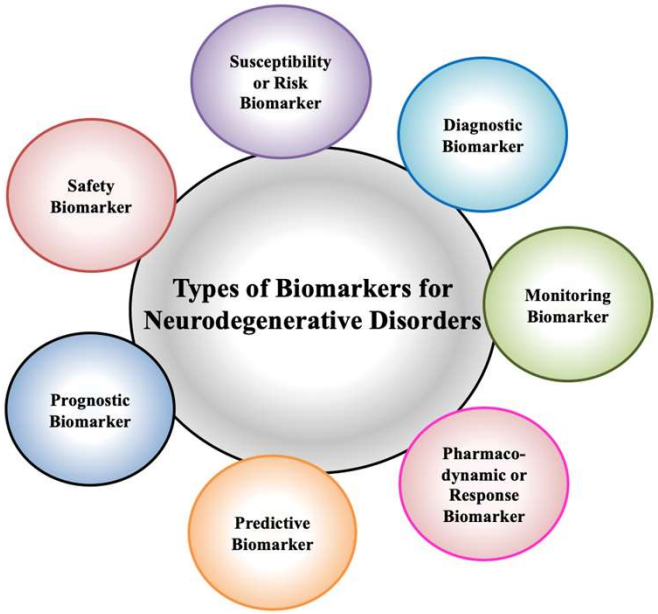


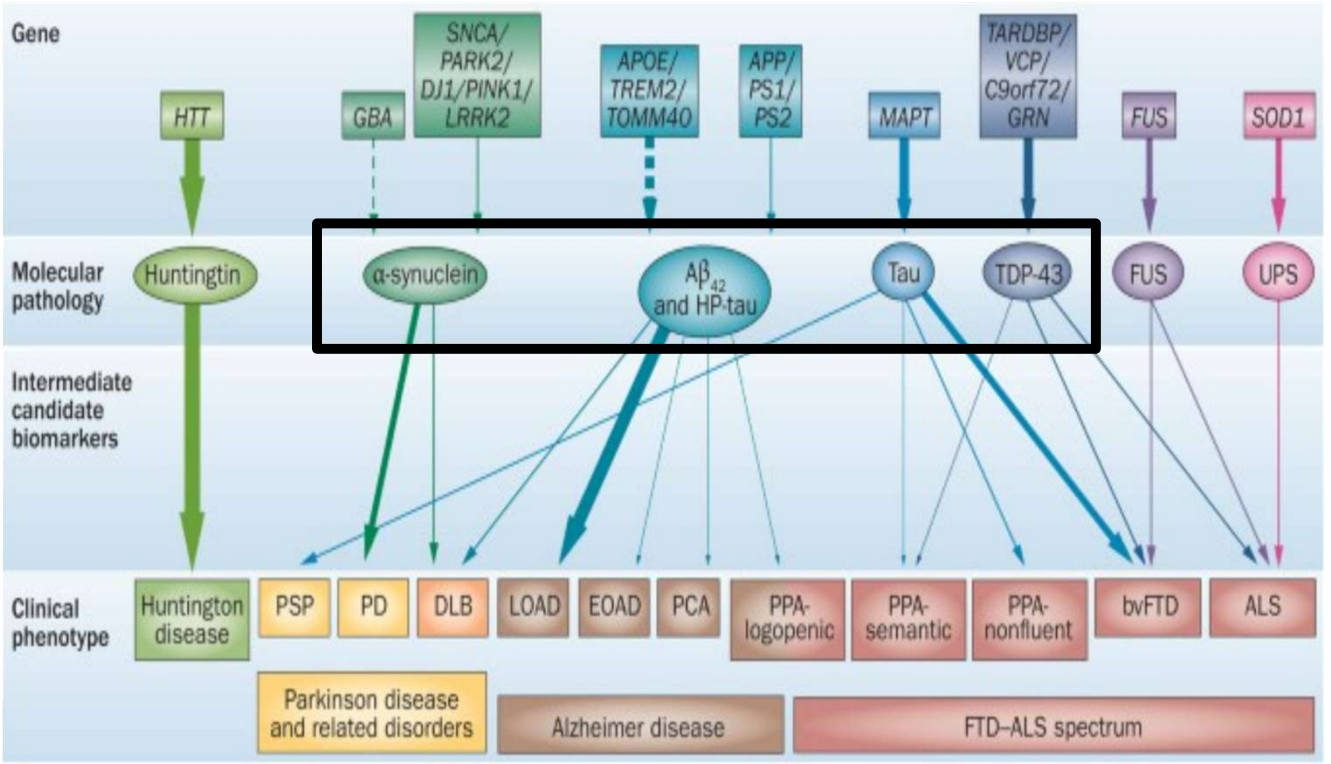
ADRD Biomarkers over time….





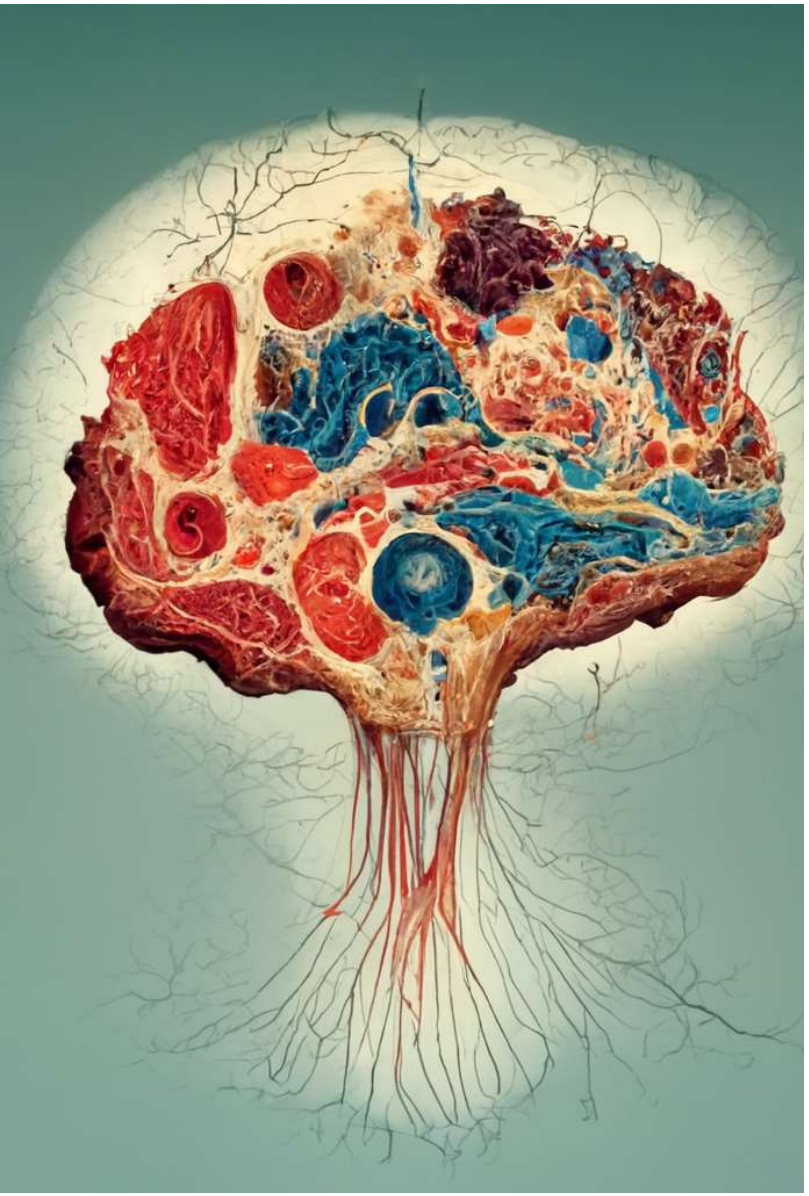
Gan et al., 2018; Liu et al., 2019; Nguyen et al., 2020; Hansson., 2021; Gong et al., 2022; Wareham et al., 2022;





*Intrinsically disordered proteins (IDP)

Pievani et al., 2014; Gan et al., 2018; Hansson., 2021

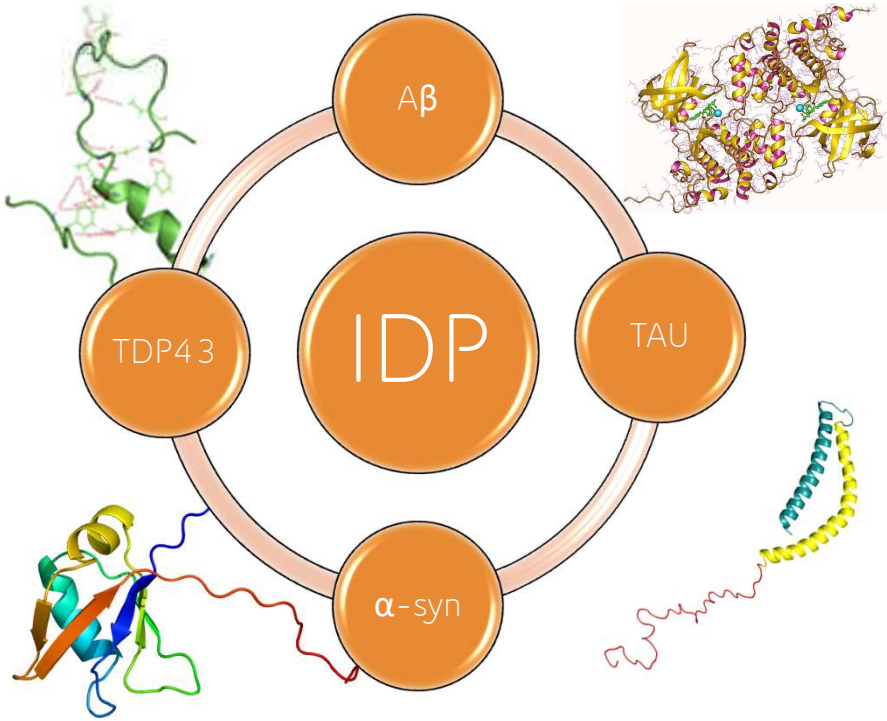


Diagnostic Protein Biomarkers

Intrinsically disordered proteins (IDP)

- Aβ, TAU, α-syn, TDP43 all IDPs

- All intrinsically disordered proteins
  - Do not, under non-denaturing conditions, form uniquely-defined three-dimensional (3-D) structures
- All have aggregation potential
  - Capacity to bind to-self
  - Capacity to bind to other proteins

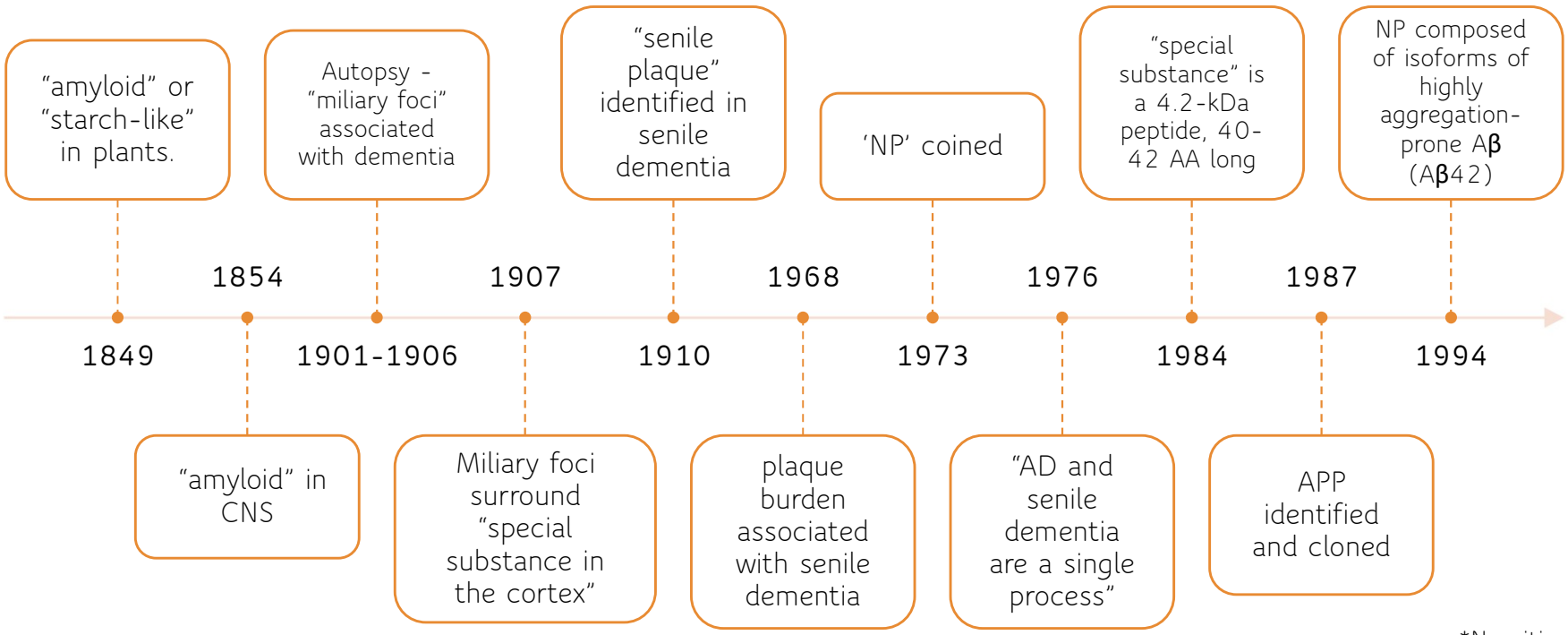


Aβ

AMYLOID-BETA FRAGMENTS

Amyloid-beta (Aβ)

History - On the Shoulders of Giants



*Neuritic plaques (NP)

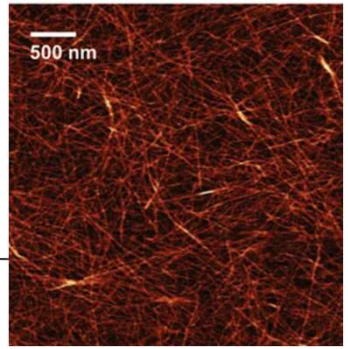
Schleiden et al., 1849; Virchow, 1854; Simchowicz, 1910; Blessed et al. 1968; Katzman 1976; Glenner & Wong 1984; Kang et al., 1987; Hardy et al., 1992; Alzheimer et al., 1995;

Amyloid
Function

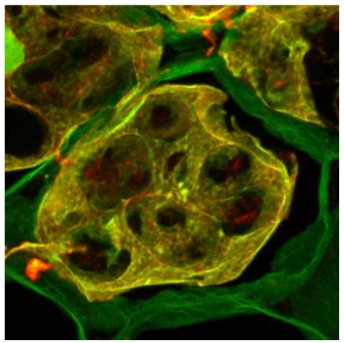
Functional amyloids and amyloidogenic peptides are common in biological systems.

- Bacteria utilize amyloids to aggregate, attach, and create biofilms
- Plants utilize amyloids as antifungal/antimicrobial and storage
- All vertebrates produce Aß with >90% sequence homology with human Aß

Conservation of the APP/Aß molecular sequence over 500 million years implies selective advantage for survival



amyloid in Staphylococcus aureus biofilms



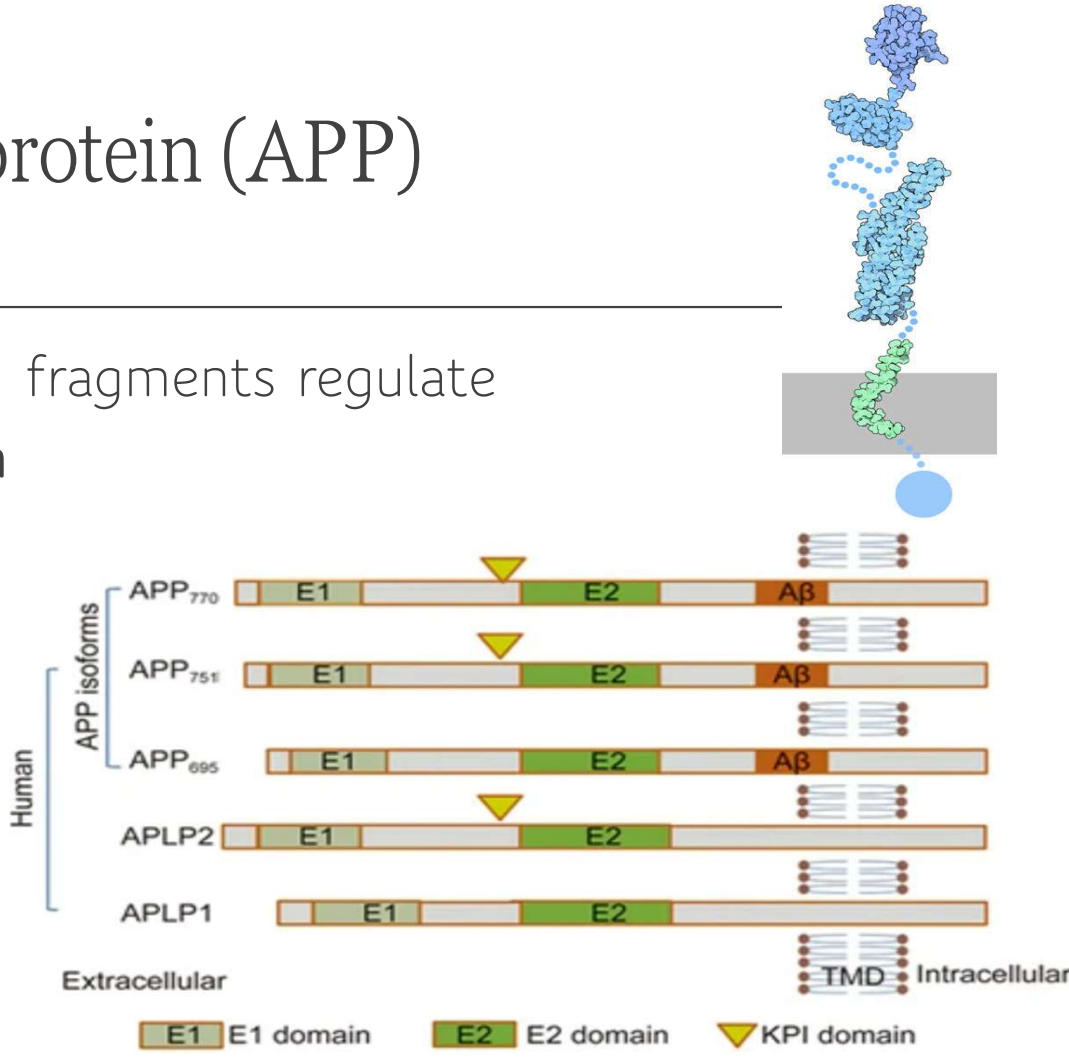
Vicilin forms amyloid-fibrils for nutrient storage in garden pea seeds

Villar-Piqué et al., 2010; Dueholm et al., 2013; Garvey et al., 2013; Bleem et al., 2017; Brothers et al., 2018; Antonets et al., 2020

Amyloid-beta precursor protein (APP)
Function

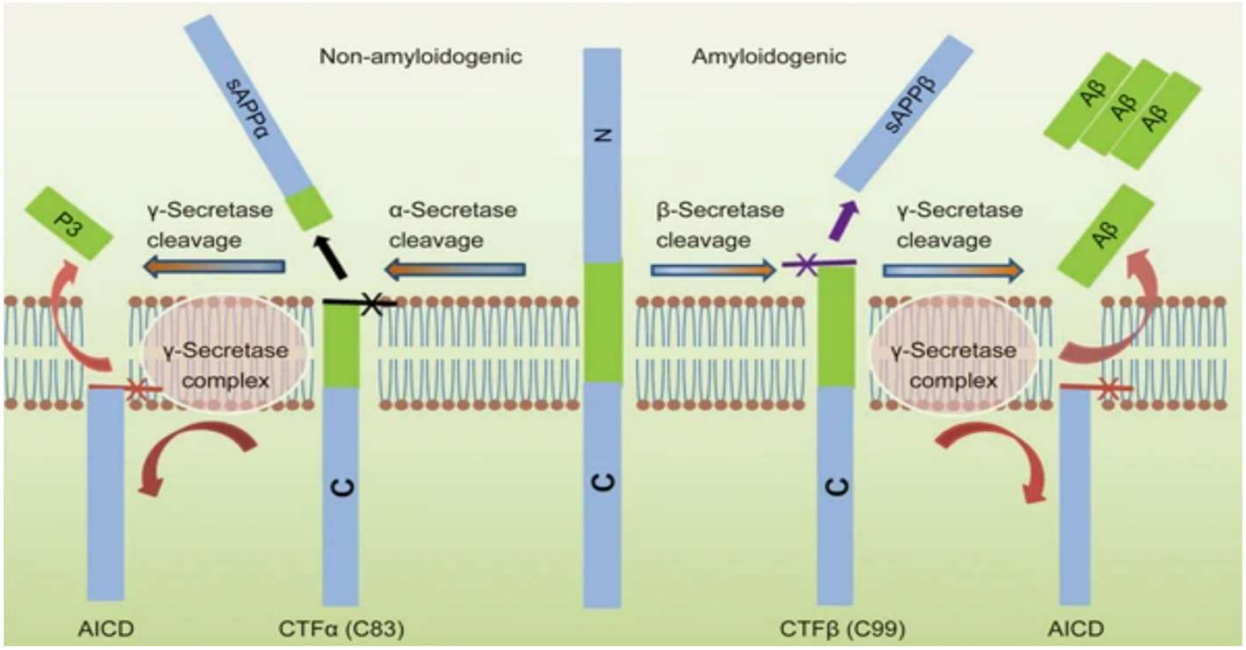
Via dedicated secretases, APP695 fragments regulate neuronal **growth, repair, and death**

- Antimicrobial/Antiviral activity
  - *"Bioflocculant hypothesis" - GV-971*
- Repairing leaks in the blood-brain barrier
  - *mAb anti-amyloid Rx associated with ARIA*
- Tumor suppression
  - *Semagacestat/Avagacestat increased skin cancer*
- Regulating synaptic function via glutamate recycling/neuroepigenetic regulation

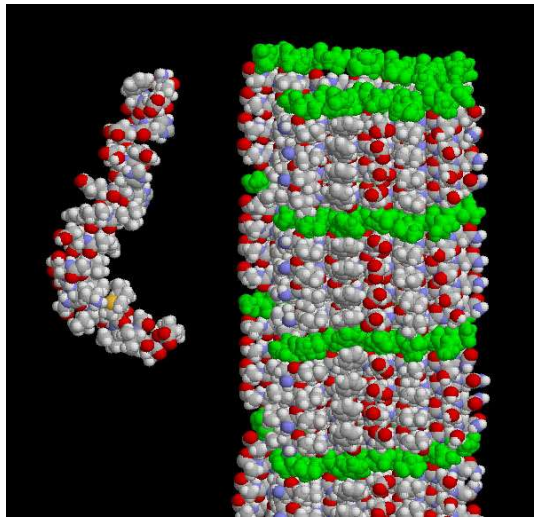


Abramowski et al., 2008; Mo et al., 2015; Chen et al., 2017; Brothers et al., 2018

Aβ (37-43 AA peptide) is a IDP derived from the transmembrane APP



"Physiological Challenge"



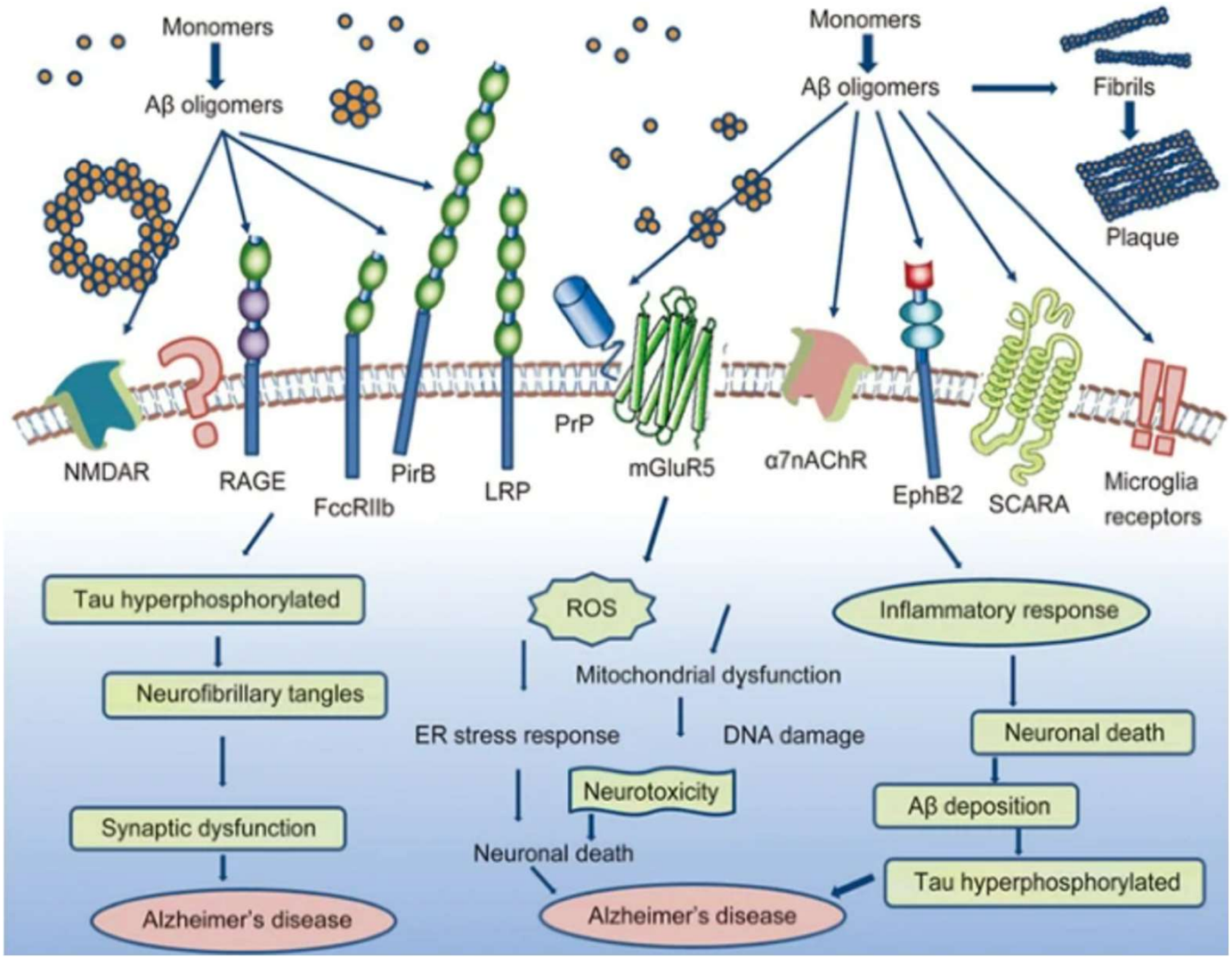
Aß42 (42 AA long)
0.75 ng/mL)

Aß40 (40 AA long)
(2-3 ng/mL)

Aβ42, Aβ43, and Aβ38 are prone to aggregate into oligomers and larger insoluble fibrils.

*Intrinsically disordered proteins (IDP)

Brothers et al., 2018



Alzheimer's Disease: The Amyloid Cascade Hypothesis

John A. Hardy and Gerald A. Higgins

nature > acta pharmacologica sinica > review > article

Published: 17 July 2017

Amyloid beta: structure, biology and structure-based therapeutic development

Guo-fang Chen, Ting-hai Xu, Yan Yan, Yu-ren Zhou, Yi Jiang, Karsten Melcher & H Eric Xu

Acta Pharmacologica Sinica **38**, 1205–1235 (2017) | Cite this article

THE AMYLOID HYPOTHESIS ON TRIAL

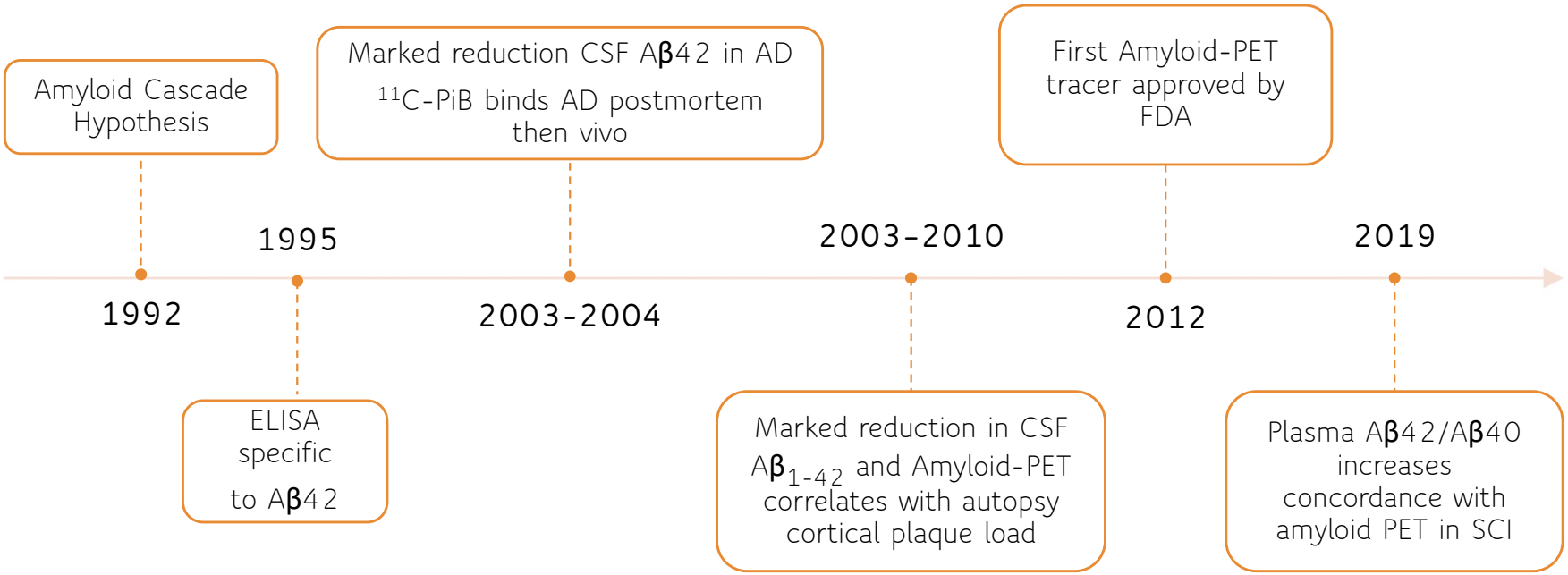
With the continued failure of potential drugs for Alzheimer's disease, is it time to look beyond amyloid-β as the root cause of the condition?

Pathological Cascade?
or
Uncontrolled Physiological Response to NOS?

Hardy and Higgins 1992; Chen et al., 2017; Brothers et al., 2018

Amyloid-beta (Aβ)

History - On the Shoulders of Giants



*Neuritic plaques (NP)

Hardy and Selkoe 2002; Blennow & Hampel, 2003; Klunk et al., 2004; Strozyk et al, 2003; Blennow et al., 2010; Hansson et al, 2019; Zetterberg et al., 2017/2019; Hansson, 2021

Amyloid-beta (Aβ)
Biomarkers – Cerebrospinal Fluid

Reduced CSF Aβ42
- 10-20 years before onset of clinical dementia
- Correlate with cortical amyloid plaque load on autopsy and Amyloid-PET

Reduced CSF Aβ42/Aβ40
- Improved correlated with Amyloid-PET and earlier detection in comparison to Aβ42 alone

Reduced Aβ43 and Aβ38
- Correlate with amyloid plaque load on Amyloid-PET

Multiple techniques and vendors with varying limitations
- Historically performance and optimal cutoffs varied substantially
- C12RMP1/C11RMP9 now used as reference methods to set CSF Aβ42 concentrations in CRM cut-offs
- Recent metanalyses now show automated platforms show similar optimal concordance with amyloid PET

Ab42, CSF	ELISA	Athena
	ELISA	Fujirebio INNOTEST
	Luminex xMAP	Fujirebio INNO-BIA
	CLEIA	Fujirebio Lumipulse
	ECL	Roche Elecsys
	ELISA	Euroimmun
	ECLIA	MSD
	Simoa	Quanterix
	SPE + LC-MS/MS	Reference Method-C12RMP1
	Isotope Dilution Mass spectrometry	Reference Method-C11RMP9
Ab42/Ab40, CSF	ECLIA	Roche Elecsys[e]
	CLEIA	Fujirebio Lumipulse[e]
	ELISA	Euroimmun
	ECLIA	MSD
	Simoa	Quanterix
	Mass spectrometry	Quest[f]
	Isotope Dilution Mass spectrometry	Reference Method-C11RMP9

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TEST ID : **ADEVL**

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Roche

FUJIREBIO Lumipulse®

Quest Diagnostics
AD-Detect™

Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring / Volume 13, Issue 1 / e12182
RESEARCH ARTICLE | Open Access

Comparing CSF amyloid-beta biomarker ratios for two automated immunoassays, Elecsys and Lumipulse, with amyloid PET status

alzheimer's association

Eline A. J. Willemse, Betty M. Tijms, Bart N. M. van Berckel, Nathalie Le Bastard, Wiesje M. van der Flier, Philip Scheltens, Charlotte E. Teunissen

First published: 01 May 2021

Strozyk et al., 2003; Buchhave et al., 2012; Palmqvist et al., 2013; Janelidze et al., 2016; Lauridsen et al., 2017; Hansson et al., 2019; Budelier et al., 2020

Amyloid-beta (Aβ)
Biomarkers – Positron Emission Topography

Detects insoluble Aβ fibrils in plaques with very high accuracy
- 11C-PiB developed as an analog of thioflavin-T

18F-PET Gold Standard in-vivo diagnosis since 2012
- 88%-98% sensitivity
- 80%-95% specificity

Clinical Correlates
- Positivity approx. 20 years before dementia onset
- Positivity ≈ higher risk for future cognitive decline
- Positivity ≈ 3-4x risk for AD in 3-5 yrs **adjusted for age
- Positivity prevalence increases linearly with age

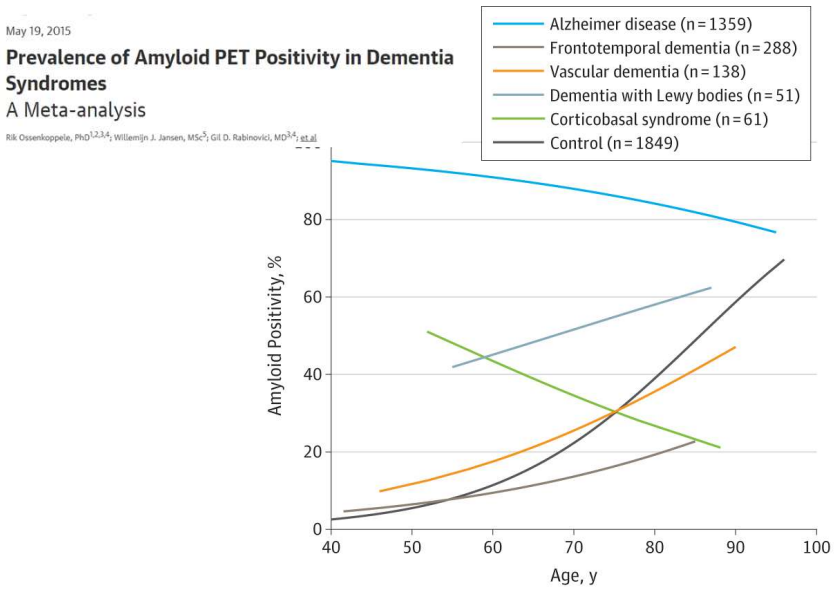
^{11}C-PiB (Investigational use; 20 min ½ life)

^{18}F-florbetapir (Amyvid) *FDA approved 2012

^{18}F-flutemetamol (Vizamyl) *FDA approved 2013

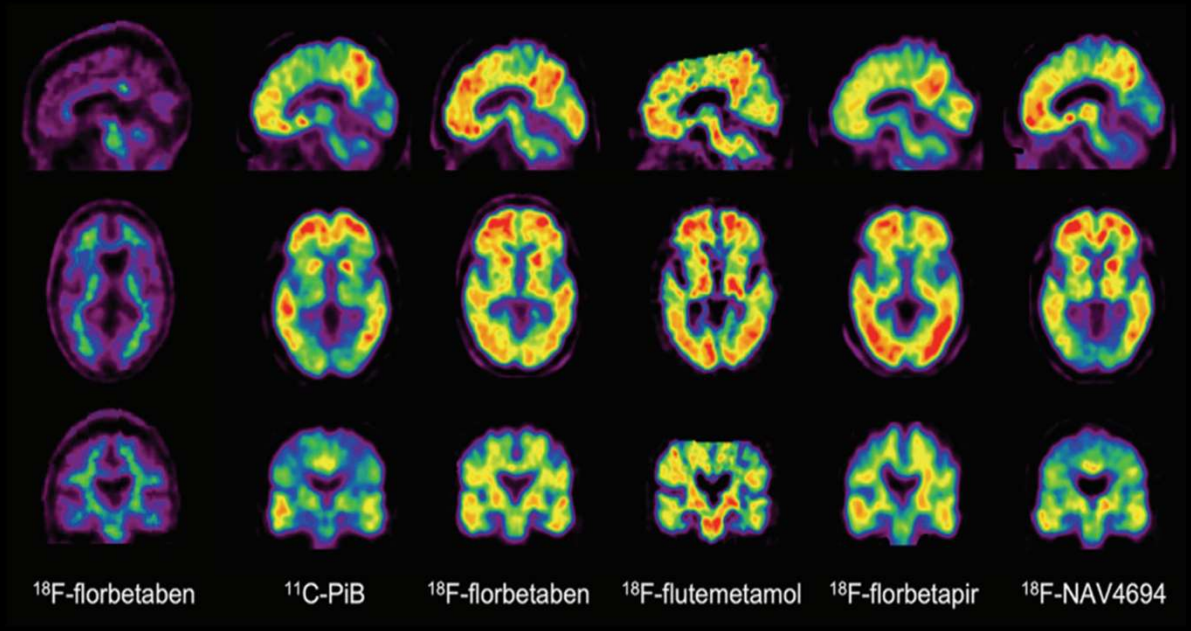
^{18}F-florbetaben (Neuraceq) *FDA approved 2014

^{18}F-NAV4698 (Investigational use)



Ossenkoppele et al, 2015; Janeiro et al., 2020; Huang et al., 2020; Hansson et al, 2019; Villemagne et al., 2021

- Amyloid PET can be interpreted as positive or negative
  - NEGATIVE - binding GM << WM
  - POSITIVE – binding GM >= WM
- Cortical retention calculation
  - SUV ratio method fast but increase FP
  - Centiloid method slow but increase TP
    - 0 = devoid of amyloid,
    - 12-25 = threshold for positivity
    - 100 =mild AD dementia



- Appropriate Use Criteria (AUC) 2013
  - Objective persistent progressive unexplained NCD
  - Meet criteria for possible AD, but *unusual*
  - Progressive dementia and early age of onset
  - NOT to assess NCD severity
  - NOT in unimpaired
  - NOT for nonmedical uses

Johnson et al., 2013; Villemagne et al., 2021; Chapleau, et al., 2022

CMS.gov

Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease

CAG-00431N

Expand All | Collapse All

Decision Summary

A. The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is insufficient to conclude that the use of positron emission tomography (PET) amyloid-beta (Aβ) imaging is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member for Medicare beneficiaries with dementia or neurodegenerative disease, and thus PET Aβ imaging is not covered under §1862(a)(1)(A) of the Social Security Act ("the Act").

2013

Original Investigation

JAMA Network Open

FREE

April 2, 2019

Association of Amyloid Positron Emission Tomography With Subsequent Change in Clinical Management Among Medicare Beneficiaries With Mild Cognitive Impairment or Dementia

Gil D. Rabinovici, MD[1,2]; Constantine Gatsonis, PhD[3,4]; Charles Apgar, MBA[5]; et al

» Author Affiliations | Article Information

JAMA. 2019;321(13):1286-1294. doi:10.1001/jama.2019.2000

J Alzheimers Dis. 2018; 63(2): 783–796.
Published online 2018 Apr 24. Prepublished online 2018 Apr 16.
doi: 10.3233/JAD-171093

PMCID: PMC5929301
PMID: 29689725

A Systematic Review and Aggregated Analysis on the Impact of Amyloid PET Brain Imaging on the Diagnosis, Diagnostic Confidence, and Management of Patients being Evaluated for Alzheimer's Disease

Enrico R. Fantoni,[a,*] Anastasia Chalkidou,[b,c] John T. O' Brien,[d] Gill Farrar,[a] and Alexander Hammers[c]

J Alzheimers Dis. Author manuscript; available in PMC 2019 Jan 8.
Published in final edited form as:
J Alzheimers Dis. 2018; 64(1): 323–335.
doi: 10.3233/JAD-180239

PMCID: PMC6323639
NIHMSID: NIHMS1000089
PMID: 29889075

Impact of Amyloid PET Imaging in the Memory Clinic: A Systematic Review and Meta-Analysis

Yat-Fung Shea,[a,b,*] Warren Barker,[a] Maria T. Greig-Gusto,[a] David A. Loewenstein,[c] Ranjan Duara,[a,d] and Steven T. DeKosky[e]

Among Medicare beneficiaries with MCI or dementia of uncertain etiology evaluated by dementia specialists, the use of amyloid PET was associated with changes in clinical management within 90 days.

Further research is needed to determine whether amyloid PET is associated with improved clinical outcomes.

iDEAS
Imaging Dementia—Evidence For Amyloid Scanning

NEW iDEAS
Imaging Dementia—Evidence For Amyloid Scanning

Rabinovici et al., 2019

Amyloid-beta (Aβ)
Biomarkers – Serum

Multiple options with varying limitations

- ELISA/Elecsys – *limitation*: Limited accuracy due to epitope masking by hydrophobic Aβ peptides, and suspicion of peripheral tissues contributing to Aβ pool
- IMR – *limitation*: Increase in plasma Aβ42 correlates with CSF **significant variability between studies**
- Simoa – *limitation*: improved accuracy but moderate association with Aβ-PET
- IP/MS and LC/MS/MS
  - Plasma Aβ42/Aβ40 has highest concordance with Aβ-PET
  - *Multiple vendors contending to be gold standard*

C_2N Diagnostics PrecivityAD™ **2020

- LC/MS/MS assay

PrecivityAD®

Quest AD-Detect™ **2022

- LC/MS/MS assay

Quest Diagnostics™

Quest AD-Detect™

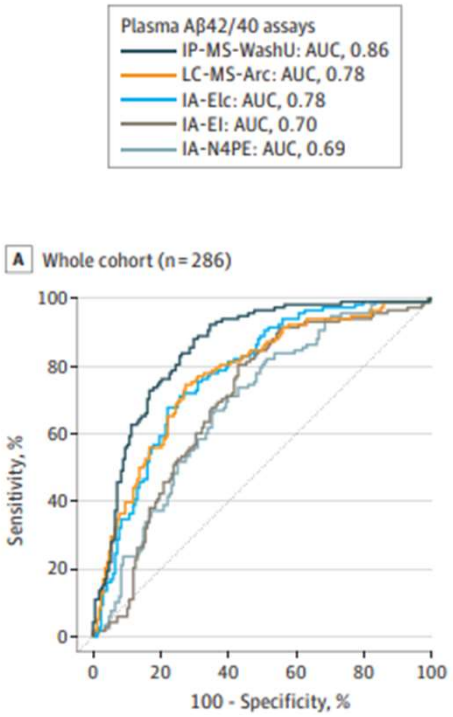
** certified for clinical use in US not FDA-approved or covered

Hansson et al, 2019; Palmqvist et al, 2019; Leuzy et al., 2022

JAMA Neurology | Original Investigation

Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease

Shorena Janelidze, PhD; Charlotte E. Teunissen, PhD; Henrik Zetterberg, MD, PhD; José Antonio Allué, PhD; Leticia Sarasa, PhD; Udo Eichenlaub, PhD; Tobias Bittner, PhD; Vitaliy Ovod, MSs; Inge M. W. Verberk, MSs; Kenji Toba, MD, PhD; Akinori Nakamura, MD, PhD; Randall J. Bateman, MD, PhD; Kaj Blennow, MD, PhD; Oskar Hansson, MD, PhD



Comparison of eight plasma Aβ42/40 assays

- Mass Spectrometry-based methods offered better precision than most immunoassays
- Roche (IA-Elc) most precise immunoassay

alzheimer's association | Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE | Open Access

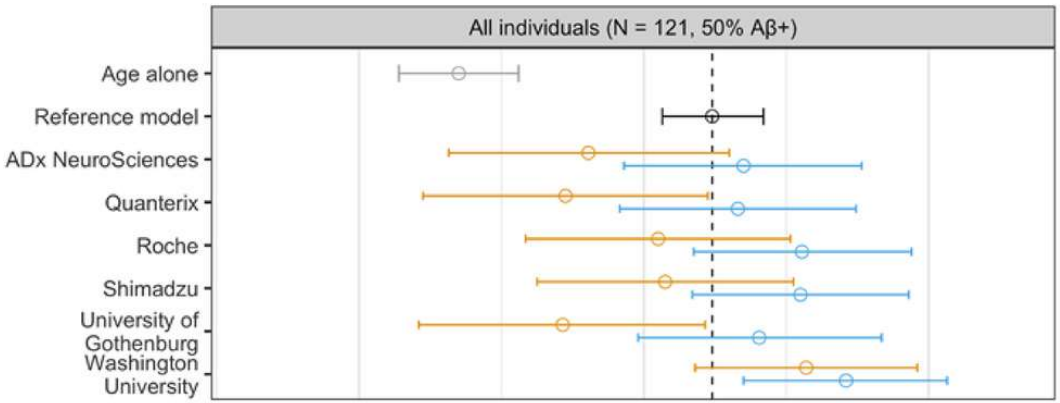
Comparative analytical performance of multiple plasma Aβ42 and Aβ40 assays and their ability to predict positron emission tomography amyloid positivity

Stephen Zicha, Randall J. Bateman, Leslie M. Shaw, Henrik Zetterberg, Anthony W. Bannon, Wesley A. Horton, Mike Baratta, Hartmuth C. Kolb, Iwona Dobler, Yulia Mordashova ... See all authors

First published: 12 July 2022 | https://doi.org/10.1002/alz.12697 | Citations: 1

Comparison of six plasma Aβ42/40 assays

- Wash U. IP-MS - AUROC 0.84
- Roche IA-Elc - AUROC 0.81
- Shimadzu IP-MS - AUROC 0.81



Janelidze et al., 2021; Zicha et al., 2022

Amyloid-beta (Aβ)
Biomarkers – Serum

Major limitation of plasma Aβ42/40 is susceptible to variation

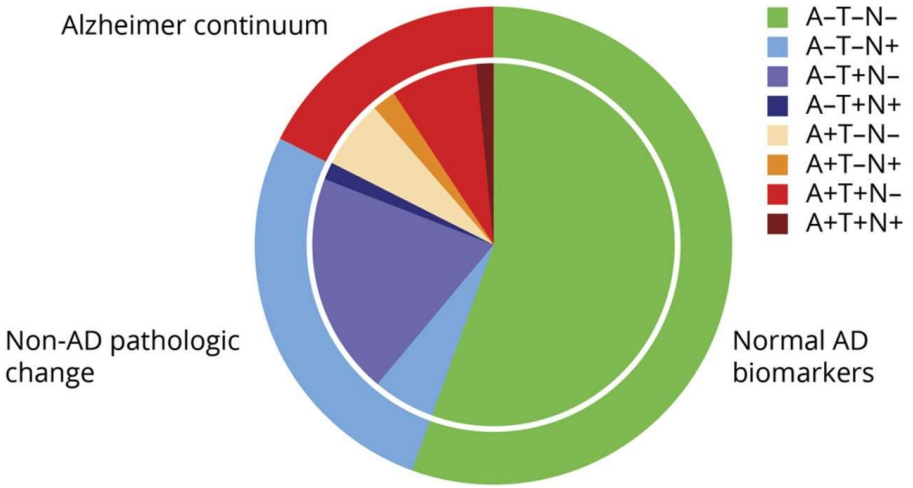
- Plasma decreased by 10-20% compared to 40-60% for CSF
- Prone to major fluctuations given peripheral metabolism/immunity, preanalytical handling/performance

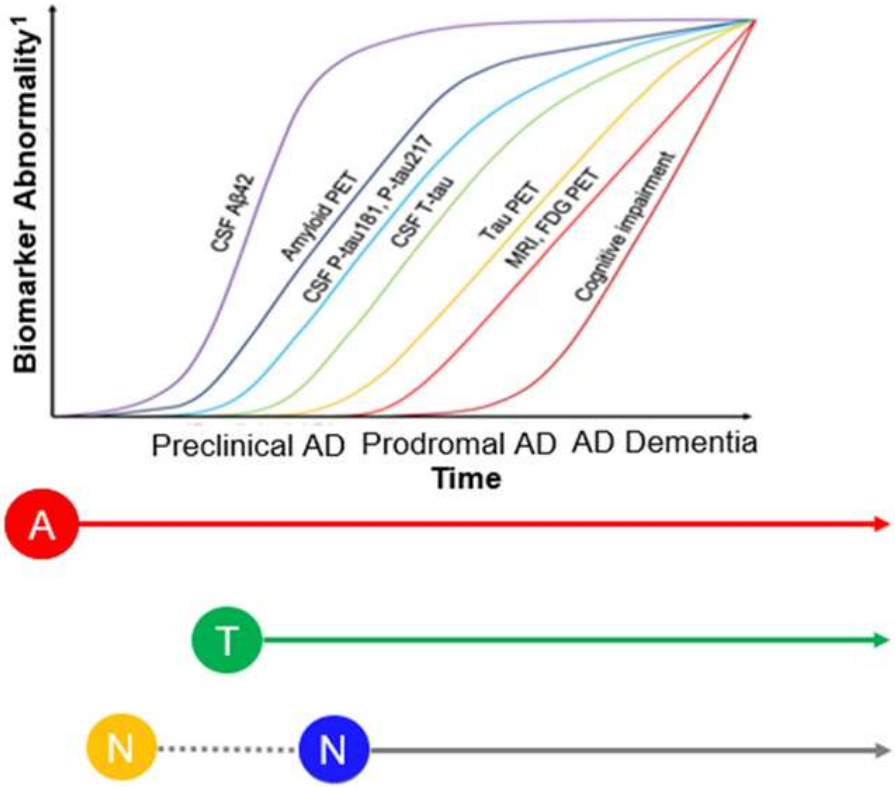
Likely only used only as a screening tool

OR to be used in combination with other biomarkers

Palmqvist et al, 2019, Schindler et al, 2019; Hansson et al, 2019; Palmqvist et al, 2019; Leuzy et al., 2022

- No single biomarker can accurately distinguish between AD clinical states
- No definite sequence of biomarker changes has been consistently confirmed in AD.





A (β-amyloid)
T (tau)
N (neurodegeneration)

Jack et al., 2016; Huang et al., 2020; Hadjichrysanthou et al., 2020; Mattason-Cargren et al., 2020; Cummings et al., 2021; Hansson., 2021

Amyloid-beta (Aβ)
Take away points

APP functions through fragments; seals, suppresses, regulates and kills

Altered Aβ fragment ratios are associated with aggregation and pathology

Amyloid Cascade is not in question - whether Aβ aggregates are the *primary* cause of AD is on trial

Amyloid-PET is Gold Standard, but CMS won't pay

CSF Aβ42 SEN/SPE assays vary by vendor but are roughly equivalent

CSF Aβ42/Aβ40 > CSF Aβ40 via ELISA/ECL
- Commercially available and covered by insurance

Plasma Aβ42/Aβ40 > CSF Aβ40 via Ultrasensitive Assays (IP/MS, LC/MS/MS)
- Commercially available but Not Covered

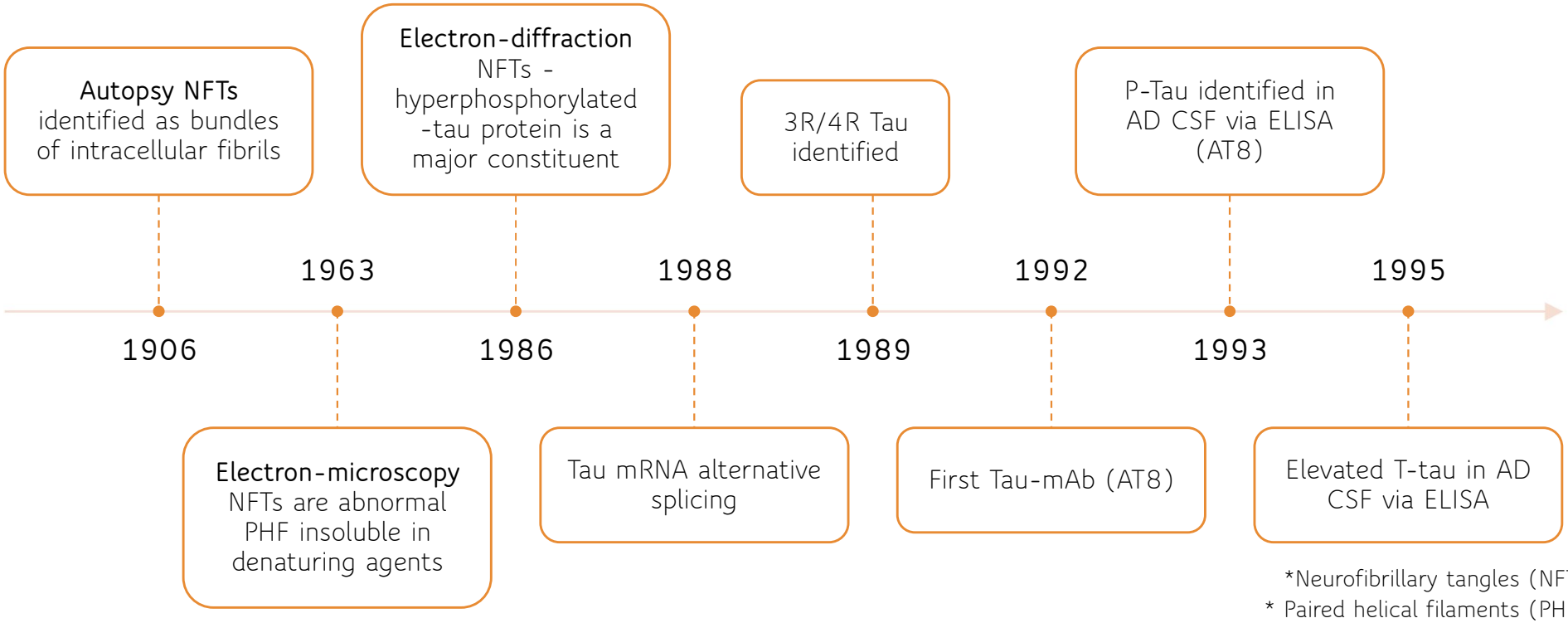
Aβ is NECESSARY but not SUFFICIENT

TAU

TUBULIN ASSOCIATED UNIT

Tubulin Associated Unit (TAU)

History



*Neurofibrillary tangles (NFT)s
* Paired helical filaments (PHF)s

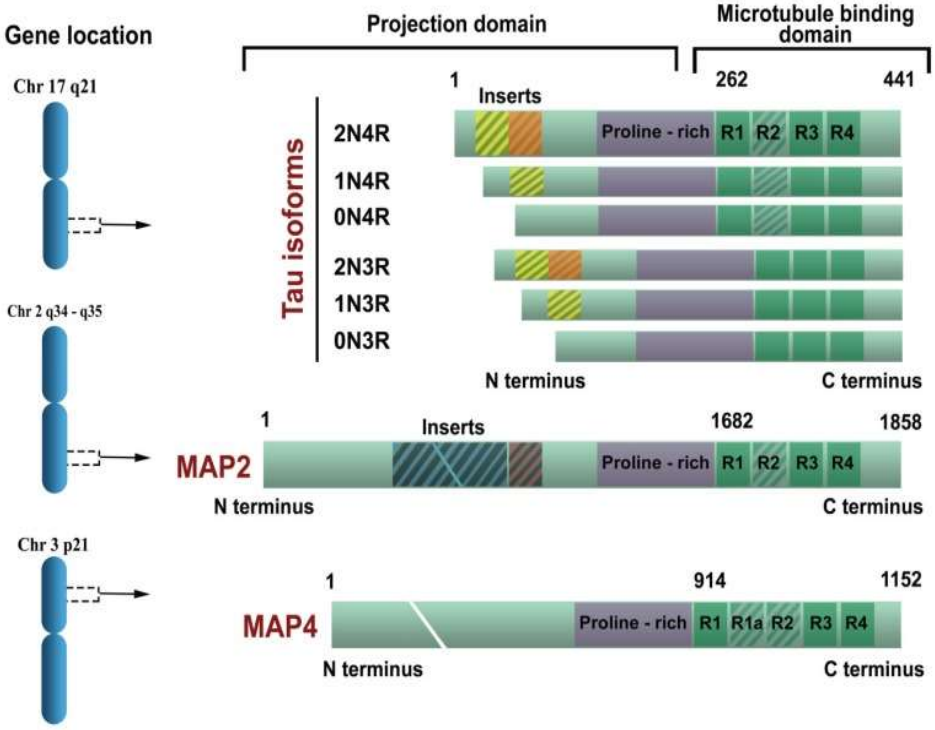
Grundke-Iqbal et al, 1986; Kidd et al., 1963; Terry et al., 1963; Biernat et al., 1992; Goedert et al., 1992; Vandermeeren et al., 1993; Blennow et al 1995

Tubulin Associated Unit (TAU)
Function

Tau is a IDP and MAP

Tau has 6 isoforms via alternatively splicing
- 3x N-terminal repeats
- 2x C-terminal 3R vs 4R repeats

Tau isoforms undergoes a 'shifts' in expression depending on stage of development, stressor, and brain region
- 4R:3R ratio shifts for MT stability vs transport dynamics



*Microtubule-associated proteins (MAP)
*Intrinsically disordered proteins (IDP)

Lovestone et al., 1997; Ballatore et al., 2007; Olsson et al., 2016; Šimić et al., 2016; Hansson., 2021

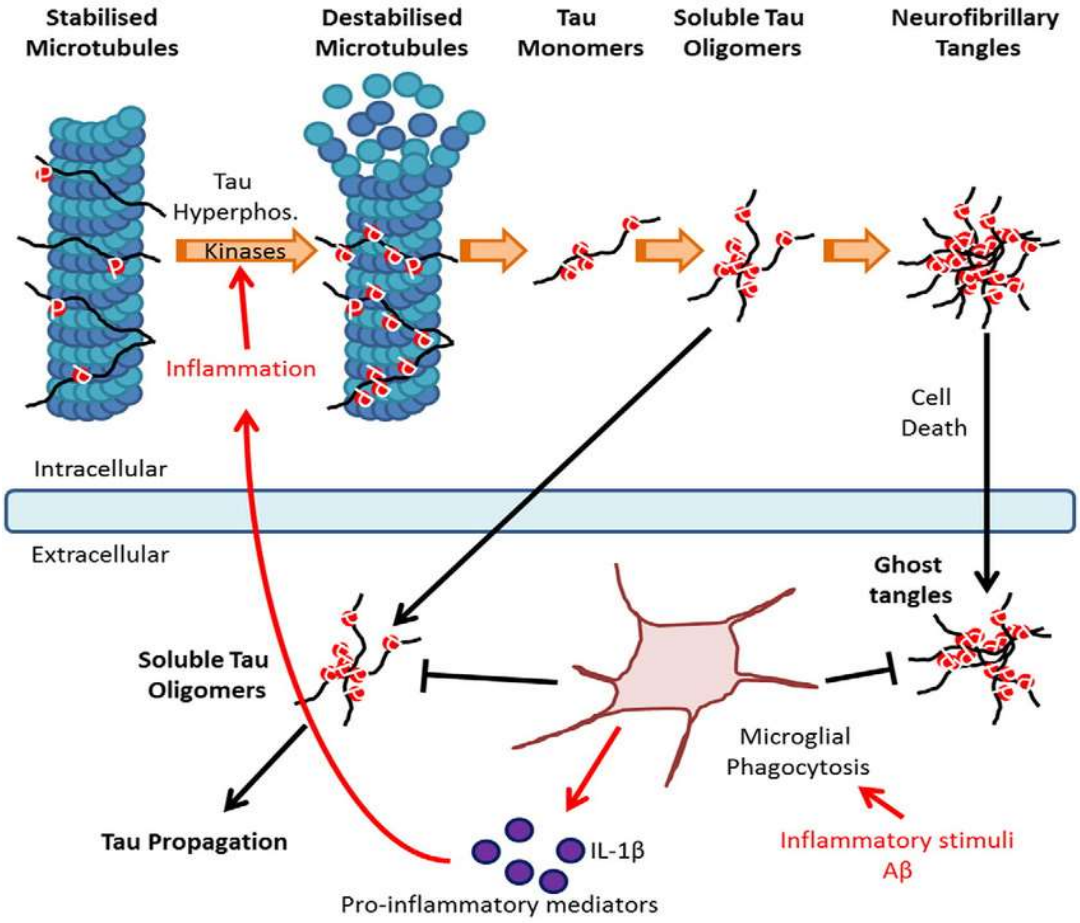
TAU Dogma

Phosphorylation

Mechanisms leading to tau pathology remains unclear and is still ***theory***

Tau acts as a scaffold protein to regulate MTs stability, assembly and spacing

- Basal phosphorylated
  - Promotes synaptic plasticity via axonal stability and transport of organelles
- Hyperphosphorylation
  - Protein detach from MT, MT remodel and compromised axonal transport
  - Increased cytosol concentration of p-tau/IDP leads to aggregation of PHTs and prion-like spread



*Intrinsically disordered proteins (IDP)
*paired helical filaments (PHFs

Weingarten et al., 1975; Brion et al., 1985; Lovestone et al., 1997; Ballatore et al., 2007; Luna-Muñoz et al., 2013; Olsson et al., 2016; Hansson., 2021;

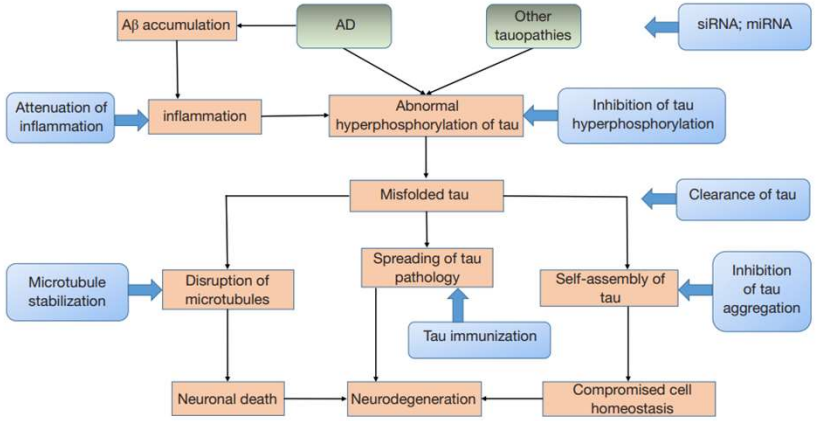
TAU Dogma

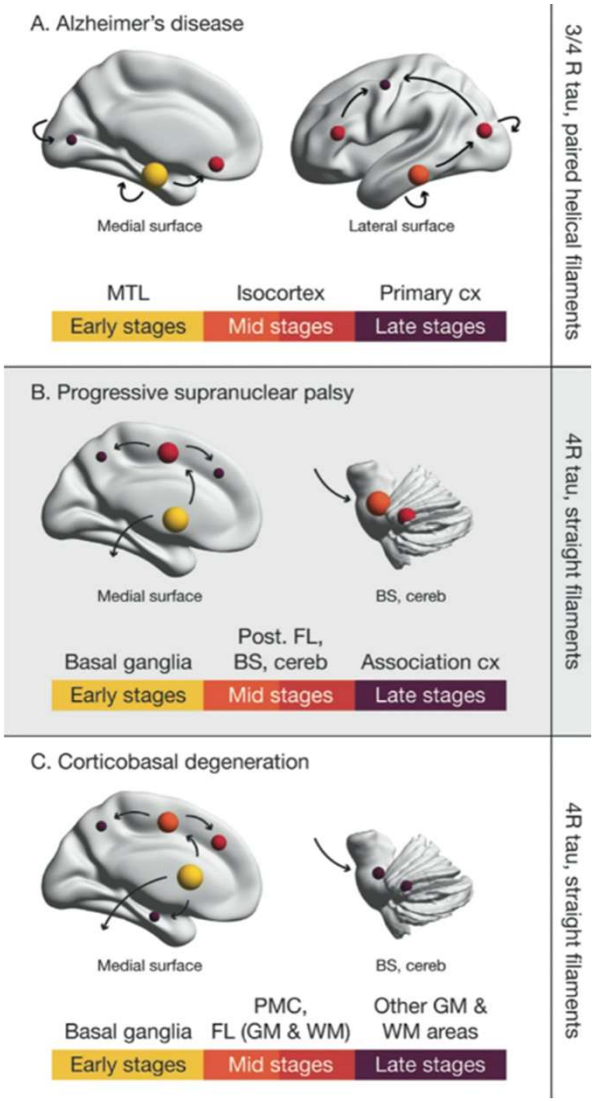
Phosphorylation

Soluble p-tau oligomers spread between cells

p-tau oligomers seed and induce further tau aggregation in recipient cell in prion-like fashion

Theory is base of current Tau-based DMT trials





Gao et al., 2018; Leuzy et al., 2019

TAU Heresy

Phosphorylation

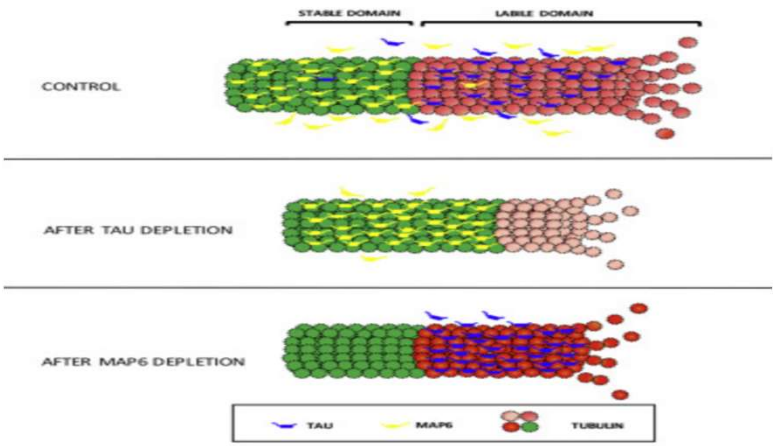
Current Biology

Volume 28, Issue 13, 9 July 2018, Pages 2181-2189.e4

Report

Tau Does Not Stabilize Axonal Microtubules but Rather Enables Them to Have Long Labile Domains

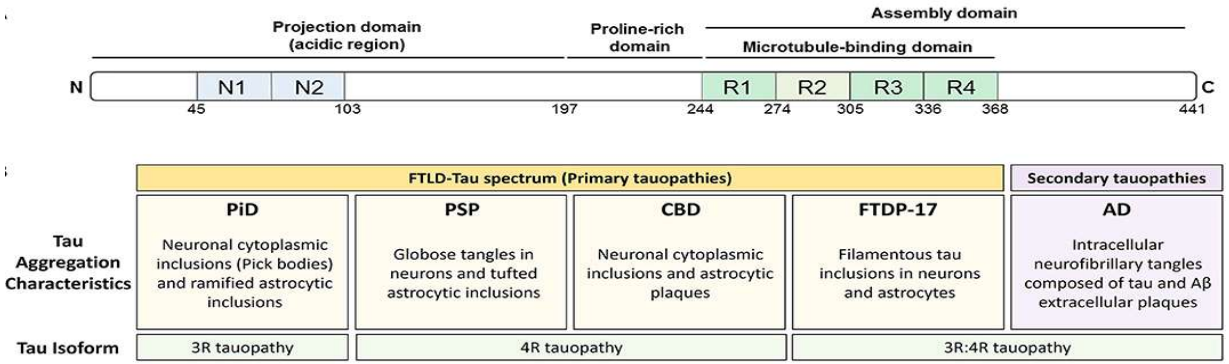
Liang Qiang [1, 2, 3], Xiaohuan Sun [1, 2, 3], Timothy O. Austin [1], Hemalatha Muralidharan [1], Daphney C. Jean [1], Mei Liu [2], Wenqian Yu [1], Peter W. Baas [1, 4]



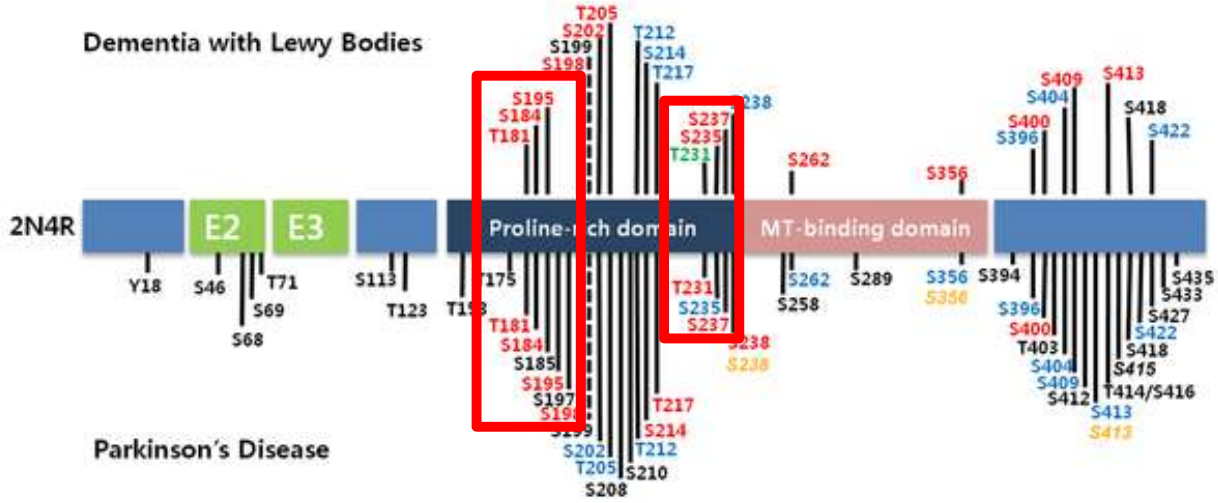
- Tau preferentially binds to labile domains of MT
- Tau depletion does not cause instability but dynamic instability
  - Hyperphosphorylation does not ***destabilize*** the entire MT, but leads to preferential loss of the dynamic regions of MT
  - MAP6 replaces tau to stabilize labile domain
- STILL a theory
- What if, Tau hyperphosphorylation may, in fact, represent part of the normal but interrupted function and catabolism of the protein.

Qiang et al., 2018; Hervy et al., 2019

- Tau is a complex protein with a variety of isoforms and fragments via PTMs*
  - Tau localization
  - Protein-protein interactions,
  - Maintenance of levels,
  - Aggregate structure.



- Tau-mediated neurodegeneration appears to be a dysregulation of disease/region/stressor/disease-stage/cell-specific PTMs
  - pTau-DLB 30% overlap with AD
  - pTau-PDD 15% overlap with AD in PFC
  - pTau-PDD 50% overlap with AD in BG

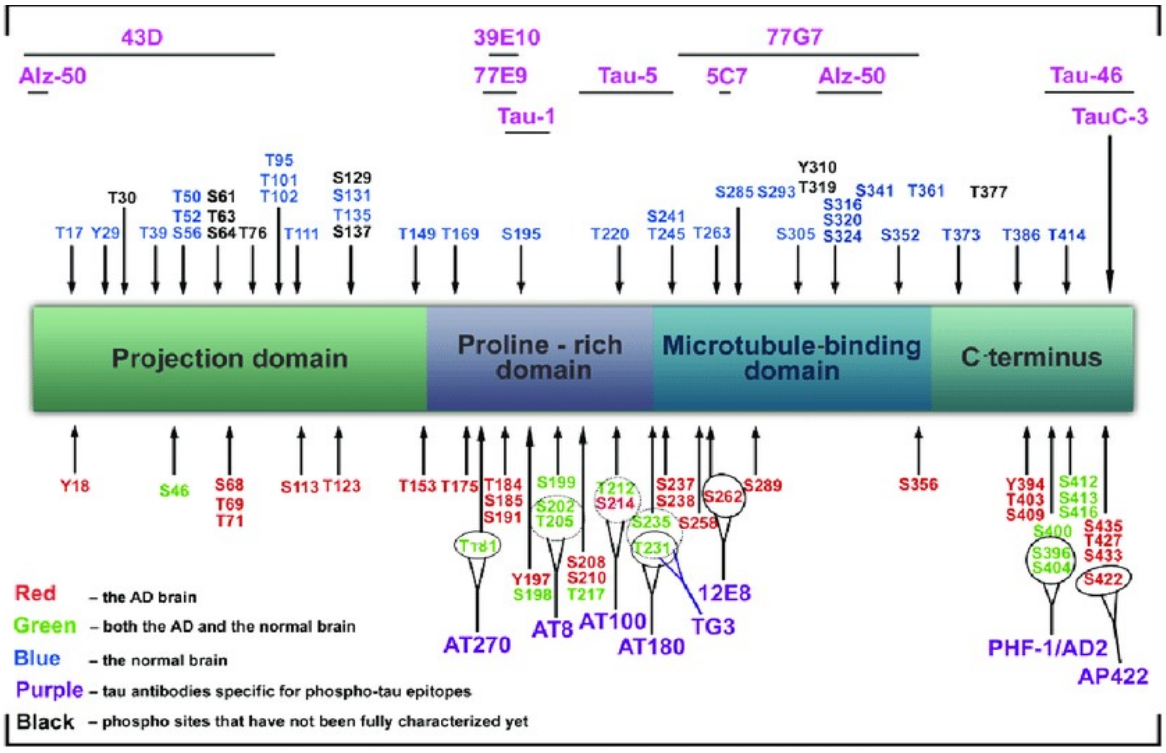


*Post-translational modifications

Duka et al., 2013; Šimić et al., 2016; Alquezar et al., 2021

Tubulin Associated Unit (TAU)

Biomarkers - Function



Tyr181 dis-inhibit motor proteins

Ser422 inhibit anterograde/retrograde axonal transport

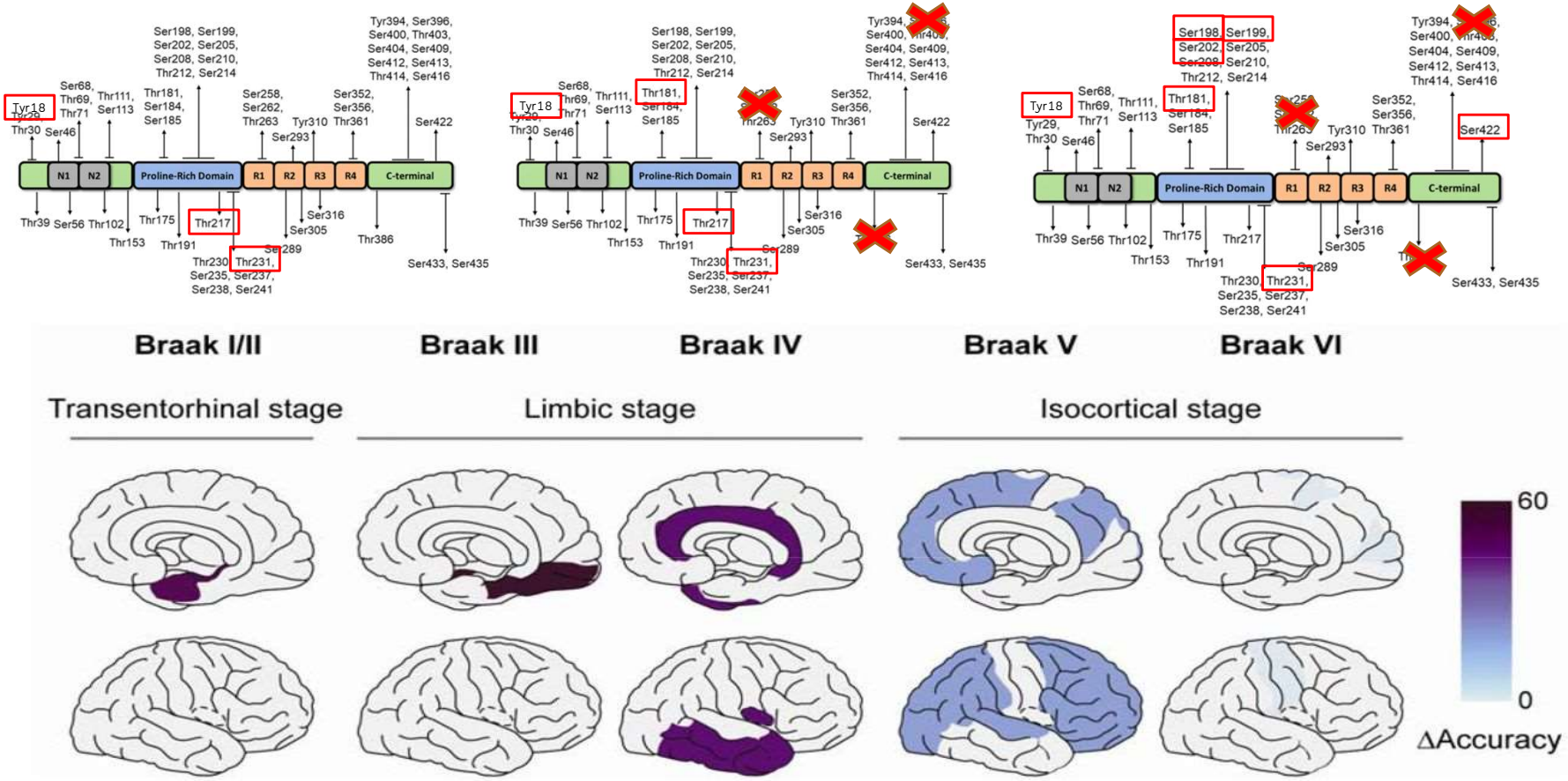
Ser231/Ser262 directly inhibit MT interactions

Thr175/Ser202/Thr205/Thr212/Ser422 promote aggregation

Thr231/Ser235/Ser262 promote seeding

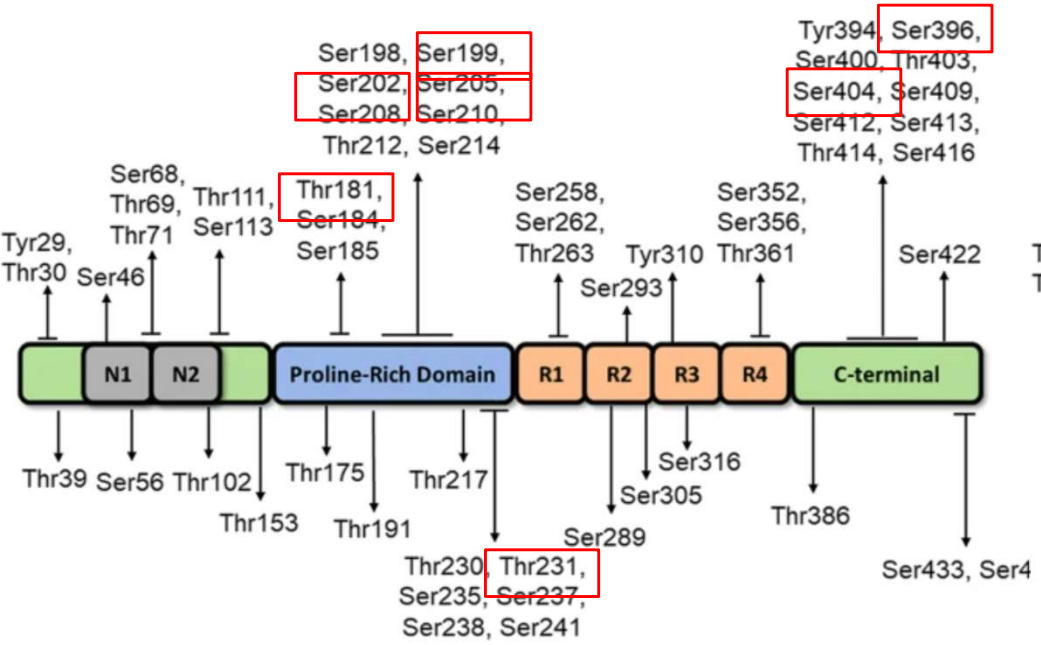
Ser198/Ser199/Ser202 + Ser400/Thr403/Ser404 decrease seeding

Sato et al., 2018; Cicognola et al., 2019; Blennow et al., 2020; Zhang et al., 2022

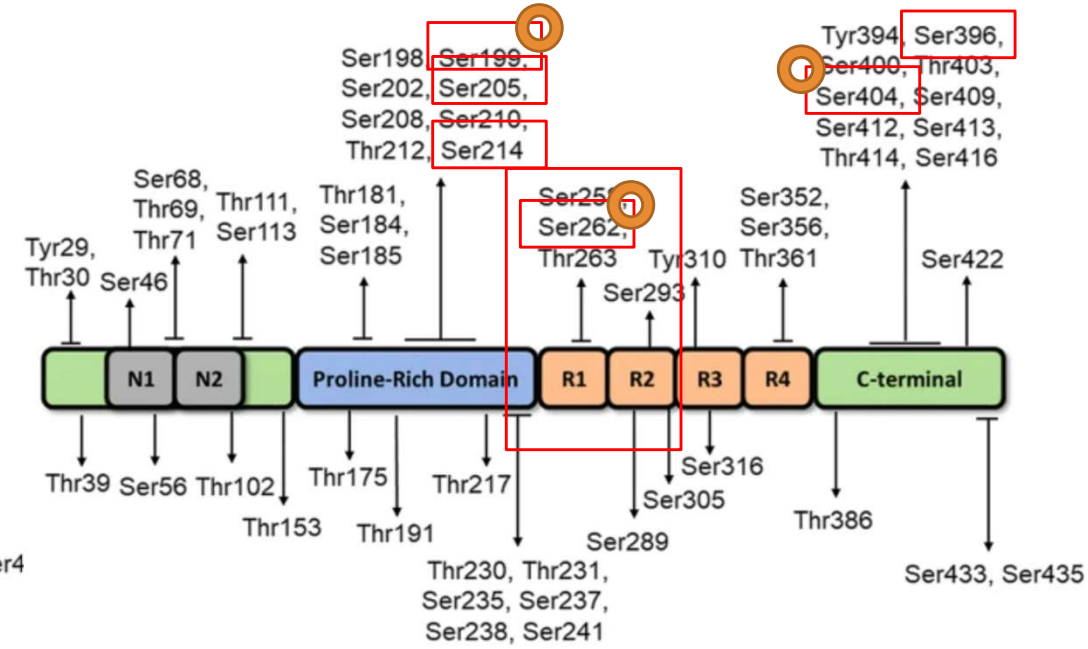


Raised t-tau and p-tau levels in AD correlated with active production and secretion from neurons in response to Aβ pathology/Braak Staging, rather than non-specific neurodegenerative process

Neddens et al., 2018; Suárez-Calvet et al., 2020



Fetal-Tau during development



Tau during Hibernation

Review | Open Access | Published: 05 June 2021

"Don't Phos Over Tau": recent developments in clinical biomarkers and therapies targeting tau phosphorylation in Alzheimer's disease and other tauopathies

Yuxing Xia, Stefan Prokop & Benoit I. Giasson

Molecular Neurodegeneration **16**, Article number: 37 (2021) | Cite this article

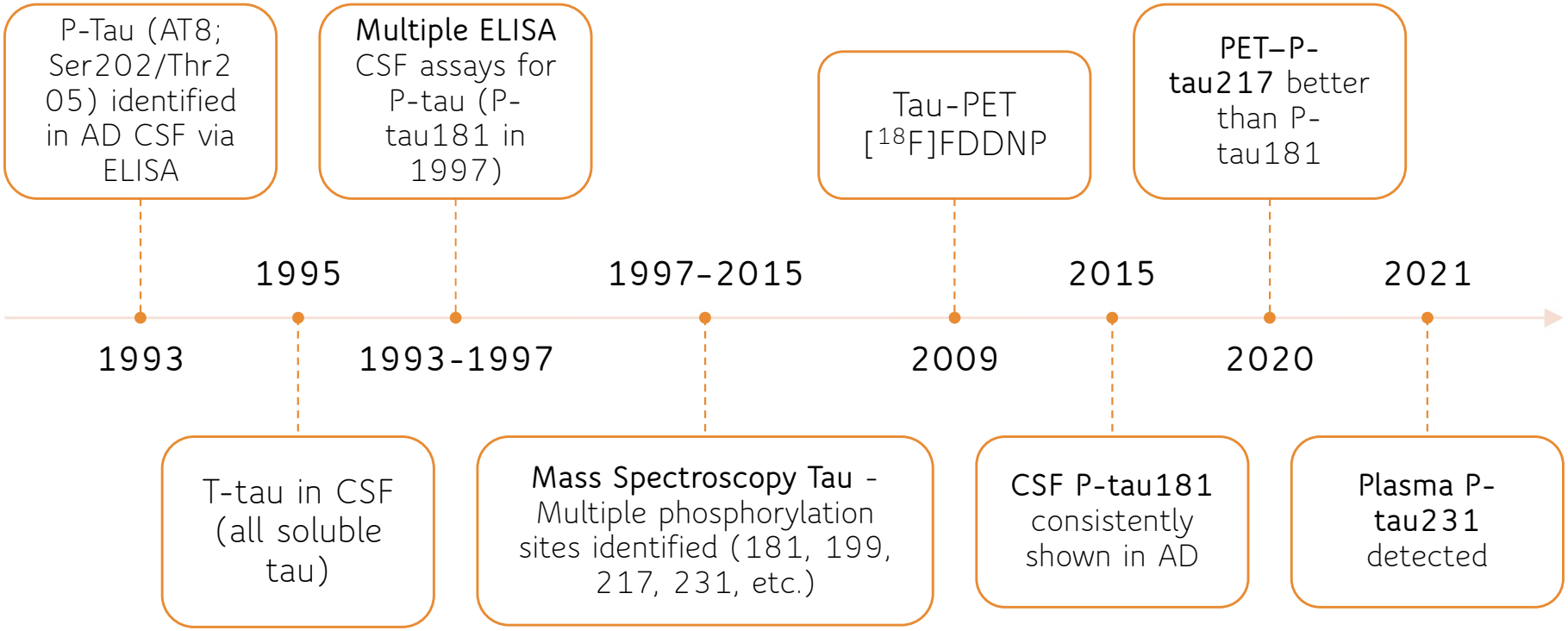
Different Tau epitope phosphorylation likely modulates localized subcellular and regional brain function

Su et al., 2008; Neddens et al., 2018; Logan et al., 2020; Xia et al, 2021

*Neurofibrillary tangles (NFT)s
* Paired helical filaments (PHF)s

Tubulin Associated Unit (TAU)

History



Grundke-Iqbal et al, 1986; Biernat et al., 1992; Blennow et al 1995; Iqbal & Grundke-Iqbal, 1997; Portelius et al, 2008; Blennow et al, 2015; Ashton et al, 2021

Tubulin Associated Unit (TAU)
Biomarkers - Cerebrospinal Fluid

mAb P-tau181 ***gold standard***
- AD vs non-AD SEN/SPE 79/96% (1.3x)
- AD vs FTLD SEN/SPE 71/97%.
- Low P-tau181/t-au in FTLD

mAb P-tau217 co-occurs with P-tau181
- AD vs non-AD SEN/SPE 91/91% (6x)
- AD vs FTLD SEN/SPE 93/88%
- Higher range than pThr181 (7.3-9.6 vs.3.6-3.7)
- Better correlation with progressive NFT

mAb P-tau231 occur before 181/217
- AD vs non-AD SEN/SPE 90/80%
- Before amyloid-PET in mOFC, precuneus and PC

	SEN	SPE	
ELISA	80%	69%	Fujirebio INNOTEST
Luminex xMAP	80%	86%	Fujirebio INNO-BIA
CLEIA	80%	83%	Fujirebio Lumipulse
ECLIA	82%	76%	Roche Elecsys

MAYO CLINIC LABORATORIES

Test Definition: ADEVL

Alzheimer Disease Evaluation, Spinal Fluid

ECLIA Roche Elecsys

athena diagnostics

ADmark® Alzheimer's Evaluation

ELISA Lab-developed test

enzyme-linked immunosorbent assay (ELISA)
electrochemiluminescence immunoassay (ECLIA).

Budelier et al., 2019; Thijssen et al., 2020; Hanes et al., 2020; Xia et al., 2021; Ashton et al., 2022

Tubulin Associated Unit (TAU)

Biomarkers - Cerebrospinal Fluid

mAb T-tau **Total or Truncated?**

- non-specific mAb to normal and abnormal Tau
- almost entirely of n-terminal soluble fragments

Commercially available immunoassays

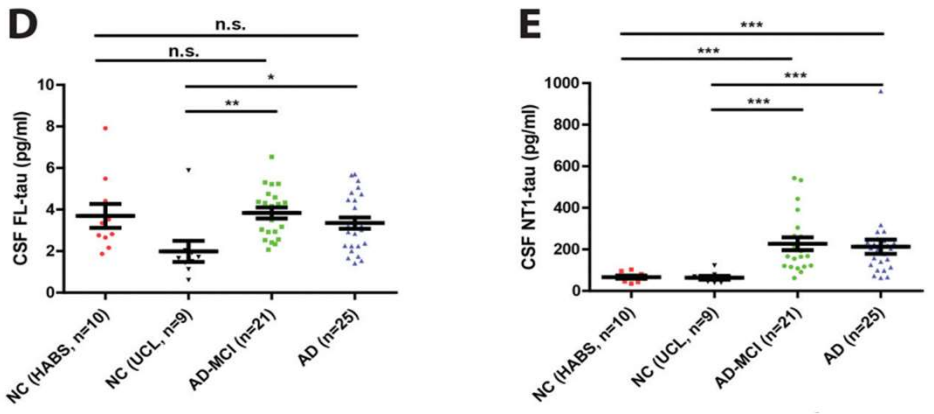
- Most recognize the mid-domain of tau
- Do not differentiate between full-length (FL) and truncated tau

t-tau elevation non-specific to neurodegeneration

- FL-tau not strong associated with degeneration
- Tau-fragments actively secreted, inconsistency in literature of NT>CT fragments

Most commonly used in literature

	SEN	SPE	
ELISA	80%	76%	Fujirebio INNOTEST
Luminex xMAP	80%	65%	Fujirebio INNO-BIA
CLEIA	75%	83%	Fujirebio Lumipulse
ECLIA	68%	83%	Roche Elecsys
ELISA	91%	79%	Euroimmun
Mass spectrometry	NA		Merck



Budelier et al., 2019; Barthélemy et al., 2019; Chen et al., 2019; Thijssen et al., 2020; Hanes et al., 2020; Xia et al., 2021

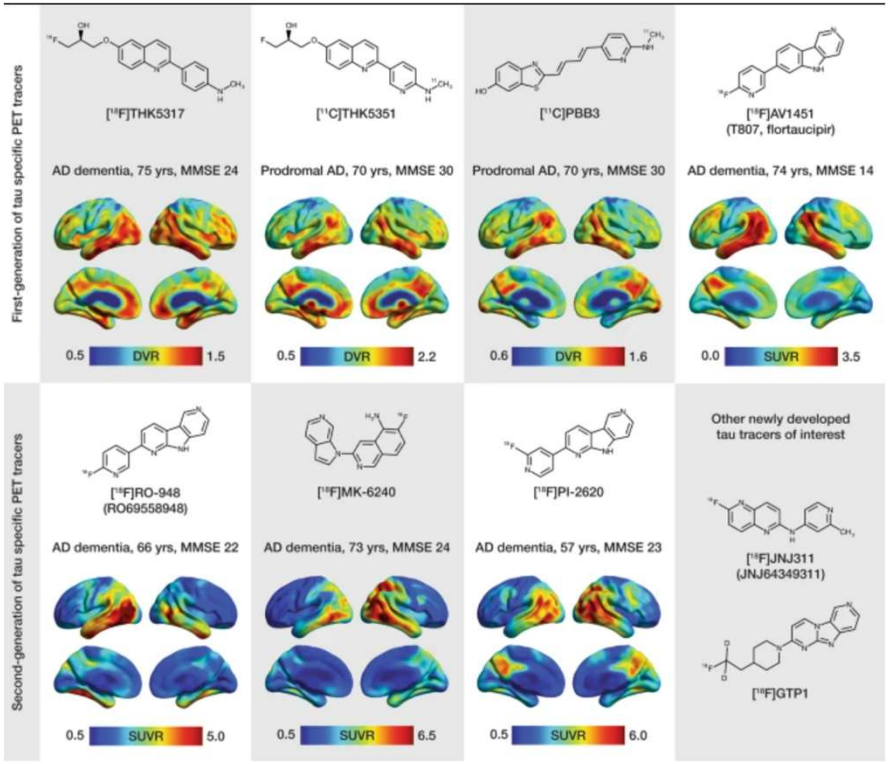
Tubulin Associated Unit (TAU)
Biomarkers – Positron Emission Topography

Tau-PET - All bind to intracellular/extracellular NFTs, NPs and ghost tangles

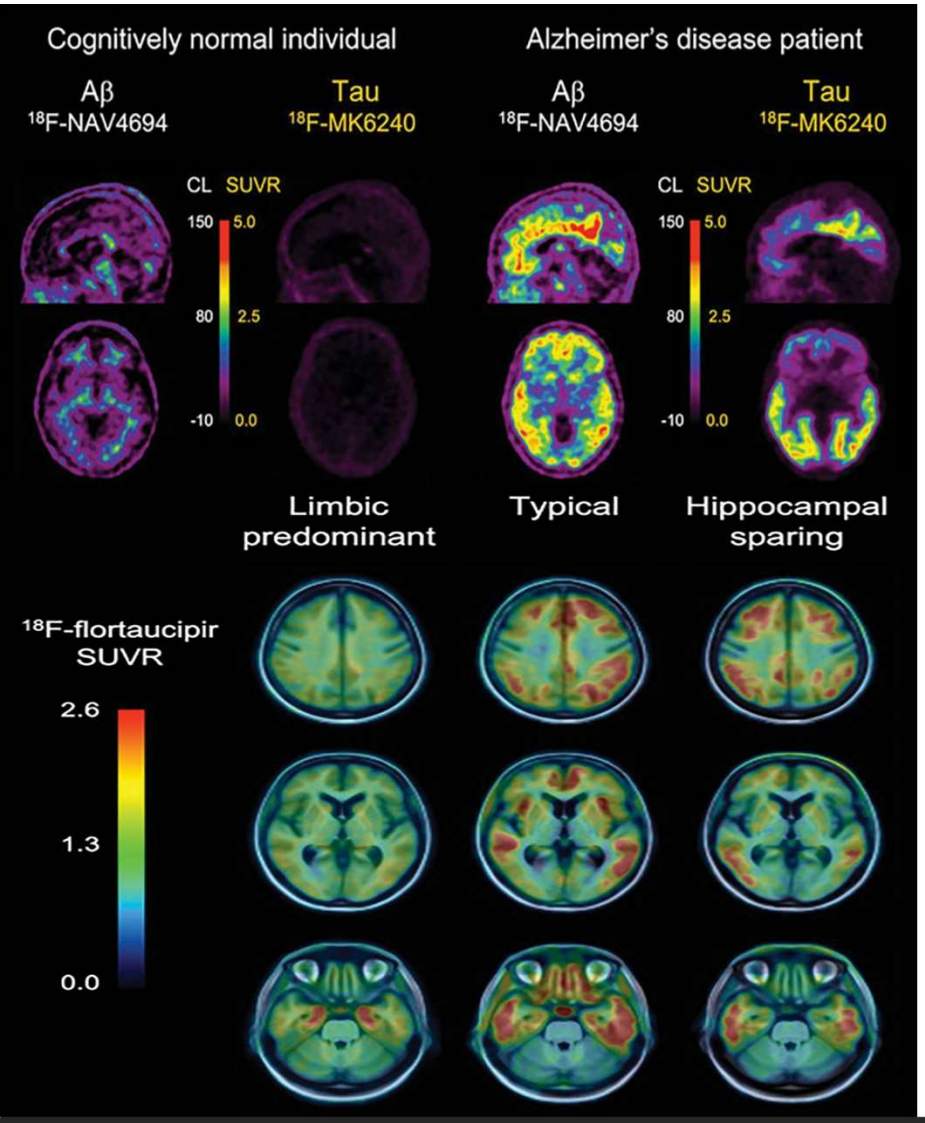
First Generation
- Significant off-target binding
- Tauvid has up to 60% non-specific signal in NC

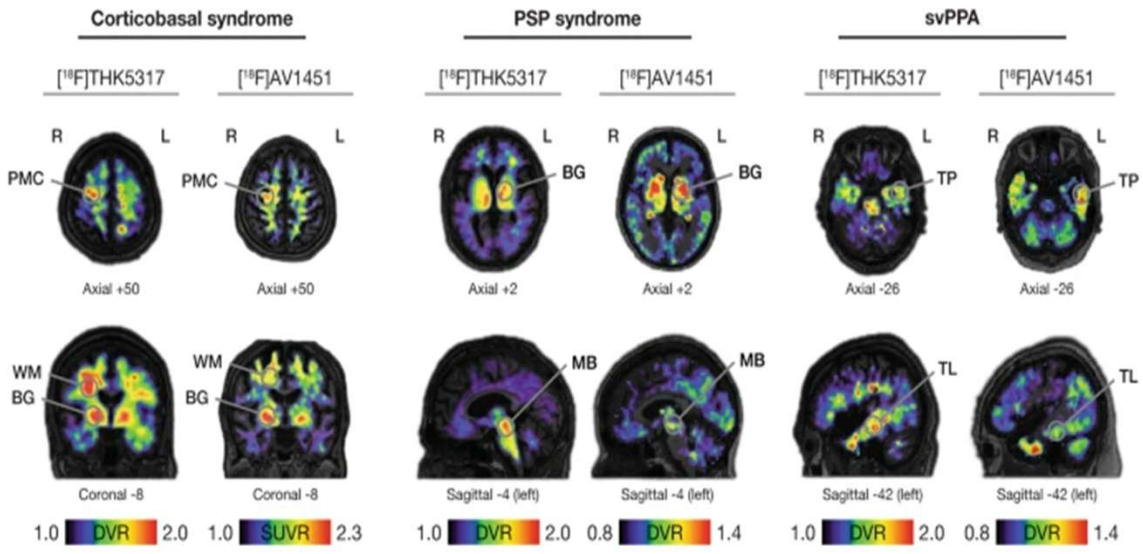
Second-generation compounds
- MK-6240/PI-2620 significantly low retention in NC
- PI2620 shown to bind to 4R tau deposits

Improved correlation with stage/symptoms
- Aid in predicting clinical progression/disease staging



Buerger et al., 2006; Wallin et al., 2010; Olsson et al., 2016; Johnson et al., 2016; Mattsson et al., 2017; Janelidze et al, 2020; Villemagne et al., 2021





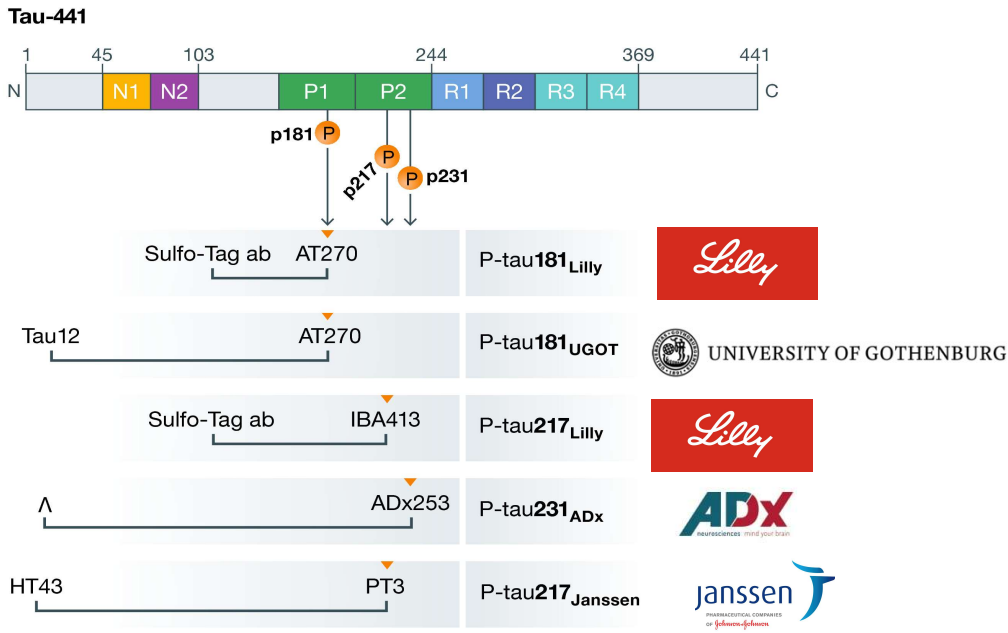
Tau	CBD	PSP	Pick's	AD	TDP-43
Isoforms	4R > 3R	4R > 3R	3R > 4R	4R ≈ 3R	Neuronal and glial deposits
Filaments	Straight >> Twisted	Straight	Twisted >> Straight	Paired helical >> Straight	Located predominantly in areas of the TL.
Deposits	Astrocytic plaques, NFTs	Tufted astrocytes, NFTs	Pick bodies	NFTs	Often asymmetric distribution (left-sided)
Location	PMC, BG, WM	BG, MB, DN	MTL, BG	MTL, TCX, neocortex	

Leuzy et al., 2019; Villemagne et al., 2021

Tubulin Associated Unit (TAU)
Biomarkers – Serum

mAb P-tau181 via Simoa
- 3.5x higher in AD vs HC
- Associated with SXS/atrophy progression at 8-years
- AD vs FTLD-tau SEN/SPE **100/63%**
- AD vs FTLD-TDP43 SEN/SPE **50/64%**

mAb P-tau217 co-occurs with P-tau181
- Less studied so unclear if significant difference yet
- 2022 Meta-analysis plasma P-tau217 more sensitive than P-tau181 to differentiate MCI-AD and AD



Molinuevo et al., 2018; Mielke et al., 2018; Palmqvist et al., 2019; Thijssen et al., 2020; Hanes et al., 2020; Xia et al., 2021; Leuzy et al., 2021; Chen et al., 2022

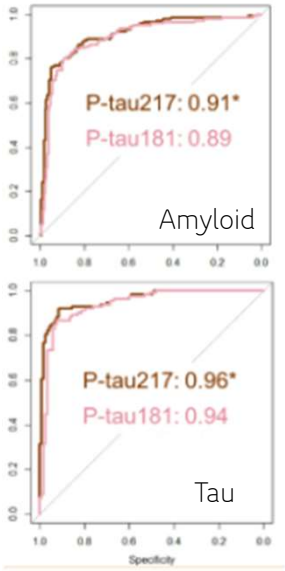
ARTICLES | VOLUME 20, ISSUE 9, P739-752, SEPTEMBER 01, 2021

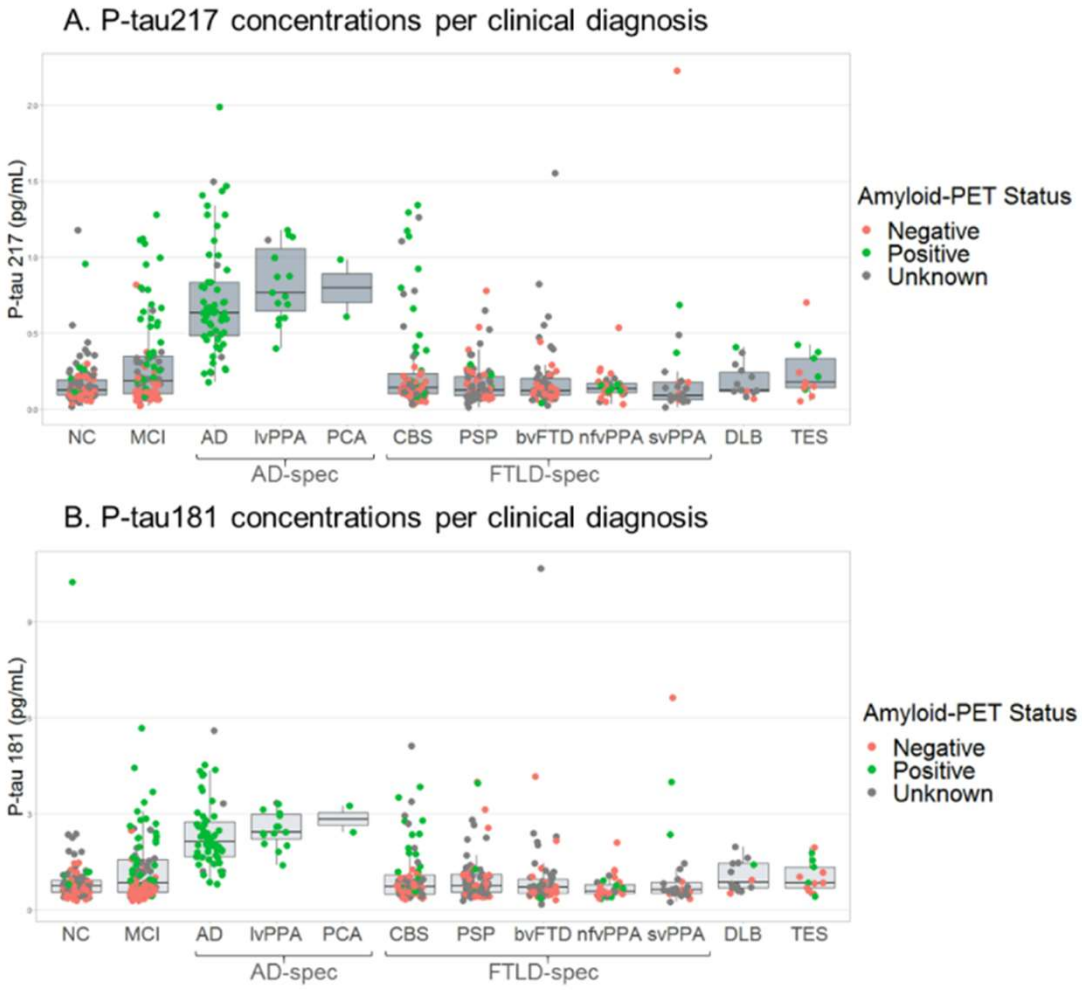
Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study

Elisabeth H Thijssen, MSc * • Renaud La Joie, PhD * • Amelia Strom, BS • Corrina Fonseca, BS • Leonardo Iaccarino, PhD • Amy Wolf, BS • et al. Show all authors • Show footnotes

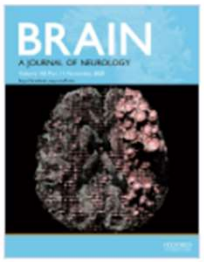
Published: September, 2021 • DOI: https://doi.org/10.1016/S1474-4422(21)00214-3 • Check for updates

- P-tau217 and P-tau181 excellent differentiating AD from other groups
- P-tau217 has minor though significantly stronger correlations with amyloid-PET and tau-PET





Thijssen et al., 2021



Volume 143, Issue 11
November 2020

JOURNAL ARTICLE

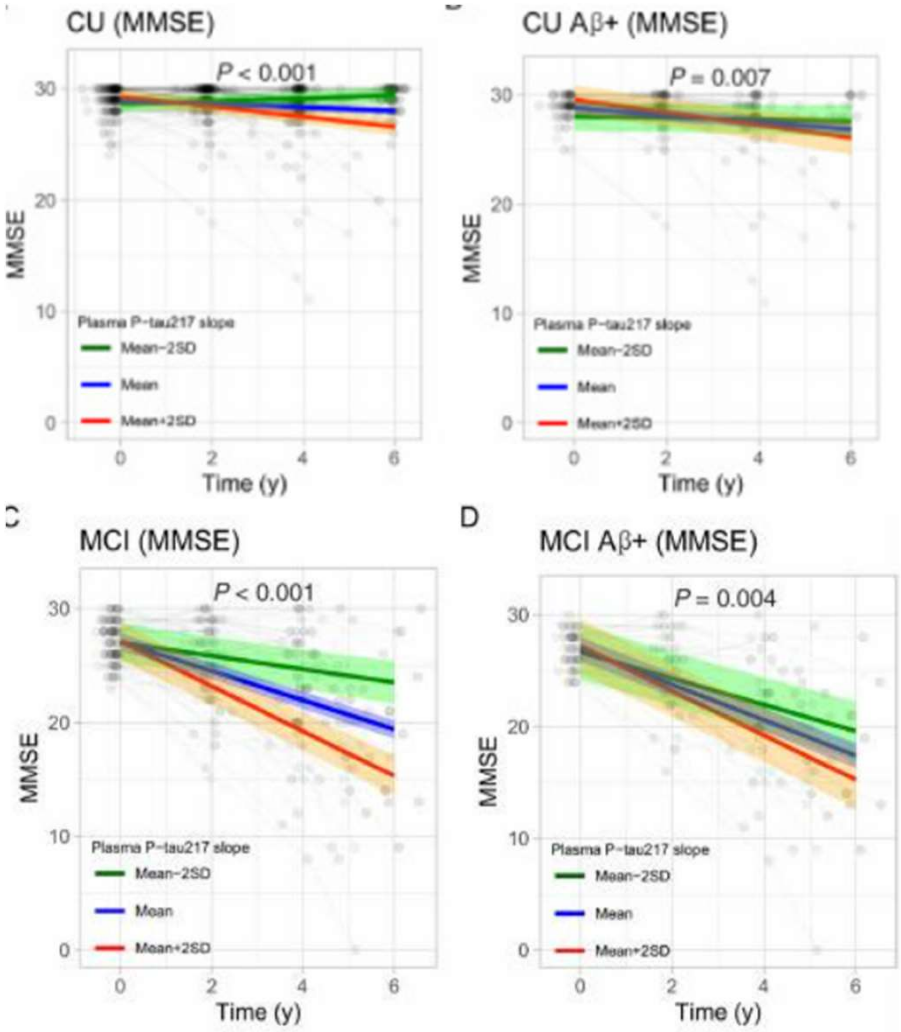
Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease

Niklas Mattsson-Carlgren ✉, Shorena Janelidze, Sebastian Palmqvist, Nicholas Cullen, Anna L Svenningsson, Olof Strandberg, David Mengel, Dominic M Walsh, Erik Stomrud, Jeffrey L Dage ... Show more

Brain, Volume 143, Issue 11, November 2020, Pages 3234–3241,
https://doi.org/10.1093/brain/awaa286
Published: 17 October 2020 **Article history** ▾

- Longitudinal (6 years) plasma p-tau217 and Nfl
  - 250 subjects (approx. age 70 [5])
  - Blood samples q2 years

- Increases in p-tau217 correlated with longitudinal worsening of cognition and brain atrophy
- Increases in p-tau217 > Nfl to monitor disease progression.



Mattsson-Carlgren. et al., 2020

Tubulin Associated Unit (TAU)

Take away points

P-Tau NOT strictly instability, but dynamic instability

Multiple fragments and exhibit different phosphorylation patterns with unclear purposes

Tau-PET correlates with symptomology better than amyloid-PET

Unless otherwise stated, CSF p-tau = CSF p-tau181

CSF p-tau217 more precise than CSF p-tau181 in AD

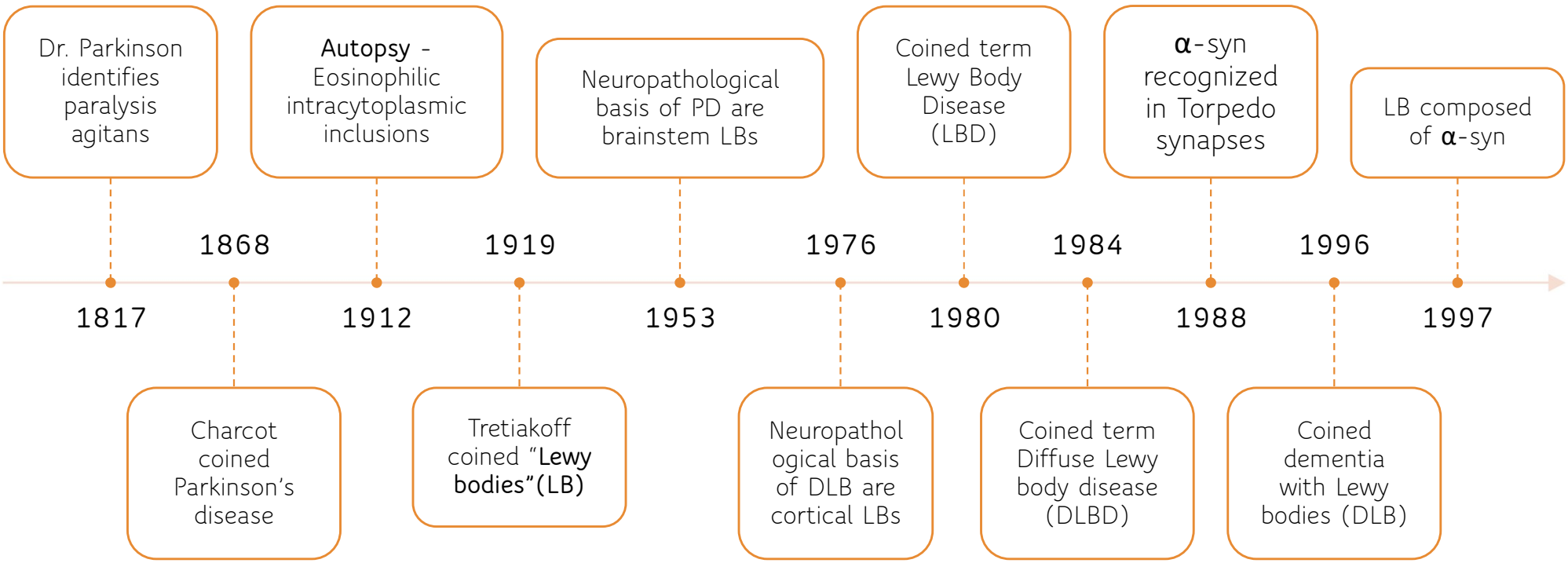
CSF p-tau231 positive before p-tau181 or CSF p-tau217 in AD

Plasma p-tau217 promising new biomarker

SNCA

ALPHA-SYNUCLEIN

α-Synuclein
History



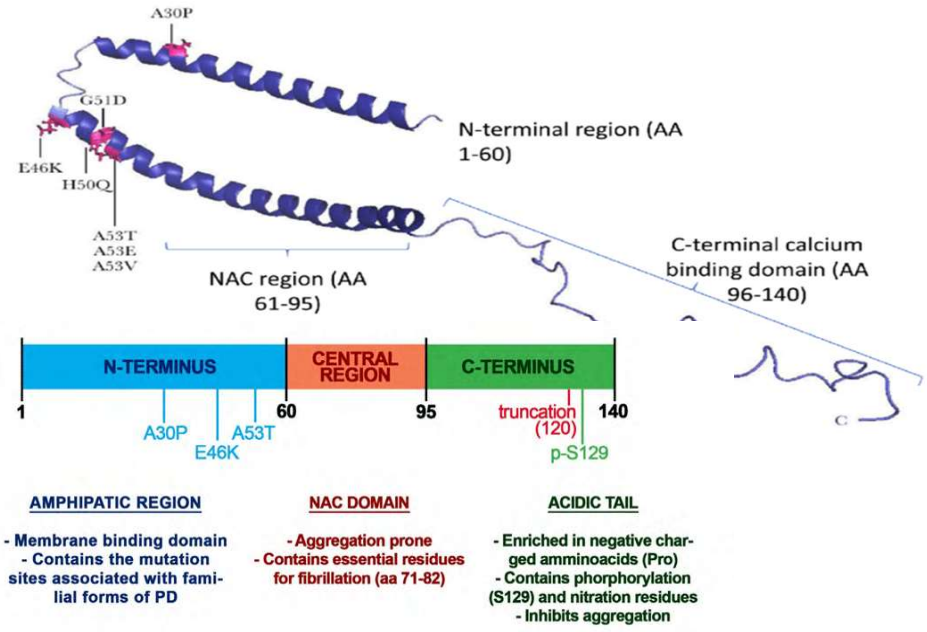
Spillantini et al., 1997; Kosaka et al., 2013

α-Synuclein
Function

Common to PD, DLB, PSA, PAD, AD

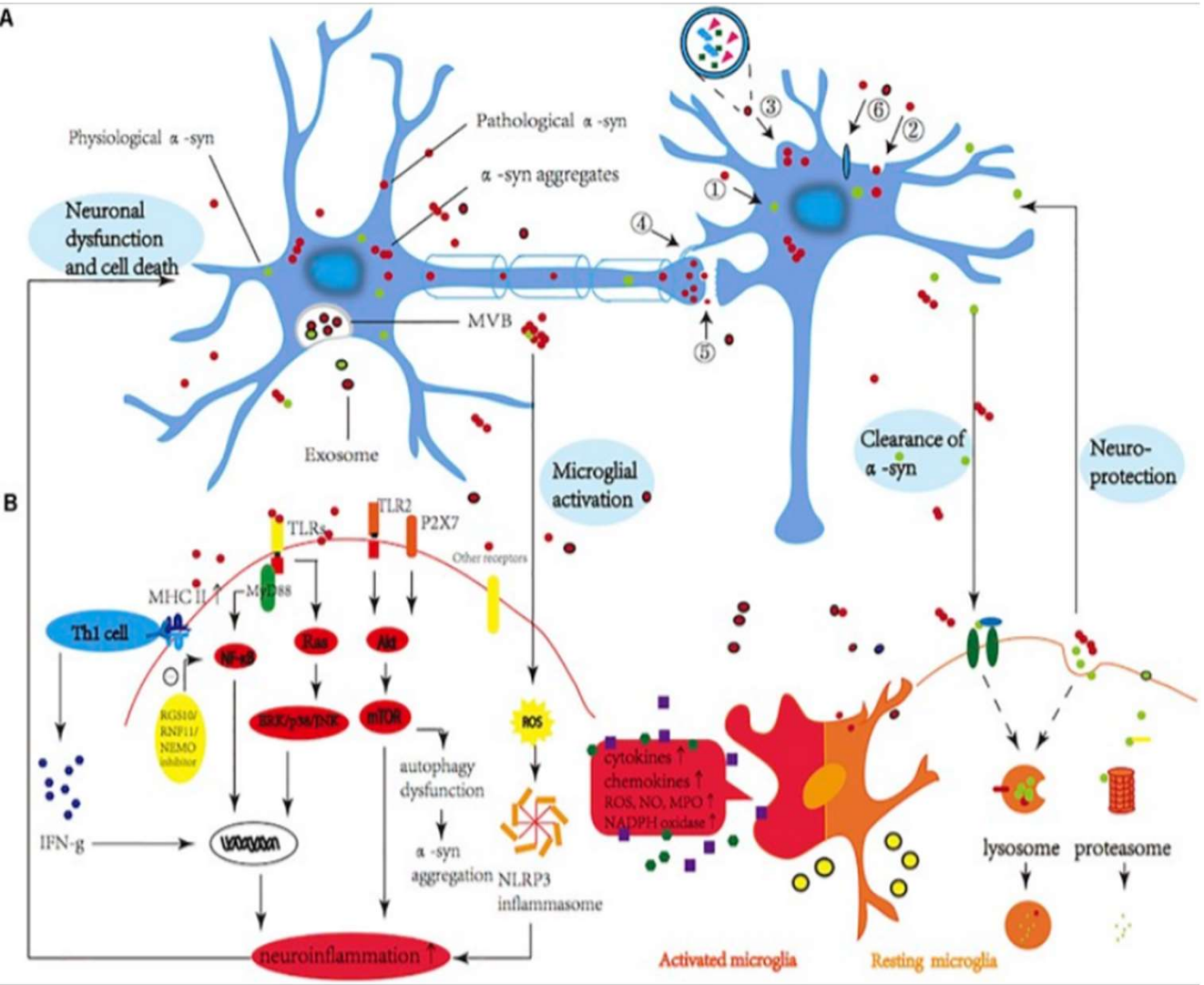
α-synuclein (e.g. synapse-nucleus)

- *SMALL* - 140 AA/15 kDa protein encoded by the SNCA gene on Chr 4q22.1
- *DISORGANIZED* – IDP and soluble
- *GETS IN EVERYWHERE* - detectable in a range of biofluids and tissues, 1% of total cytosolic protein
- UNTETHERED, IT CAUSES PROBLEMs



*Intrinsically disordered proteins (IDP)

Maroteaux et al., 1988; Stefanis et al., 2012; Poewe et al., 2017



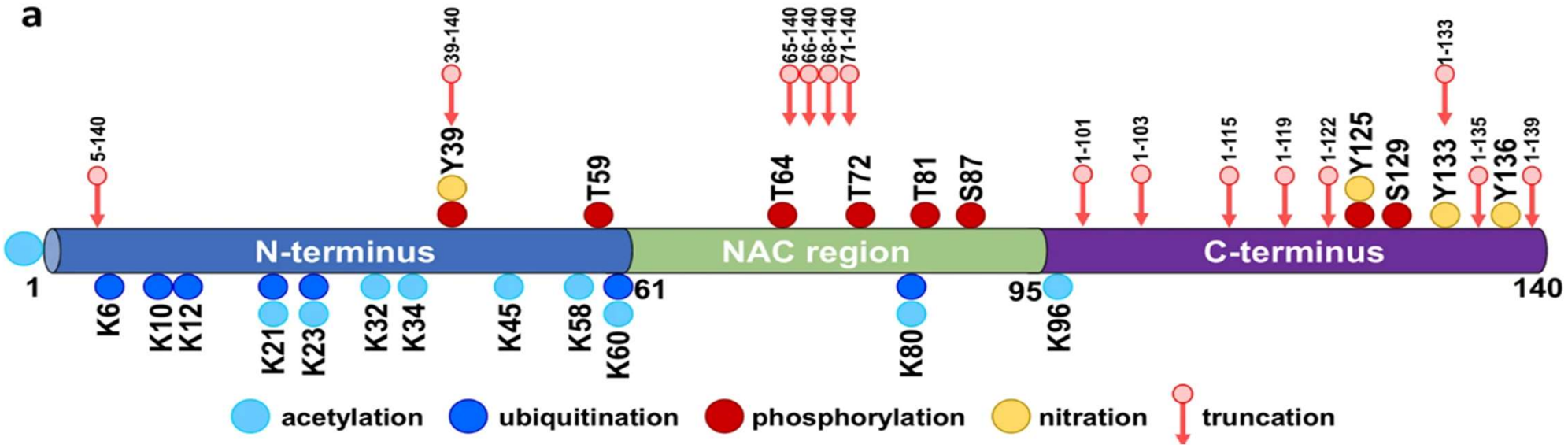
Physiological function of α-syn is only *partially* understood and *still controversial*

- Involved in biosynthesis, maintenance, exocytosis of *vesicles/exosomes* allowing **prion-like** spreading

Aggregation of monomers → oligomers → spherical, chain-like, annular (pore-like) and tubular

- *SEED*: Oligomers to form β-sheet of fibrillar aggregates linked to cytotoxicity
- *CROSS-SEED:* Fibrillar aggregates protein complexes (tau and Aβ) creating LB with α-syn in core

Zhang et al., 2018



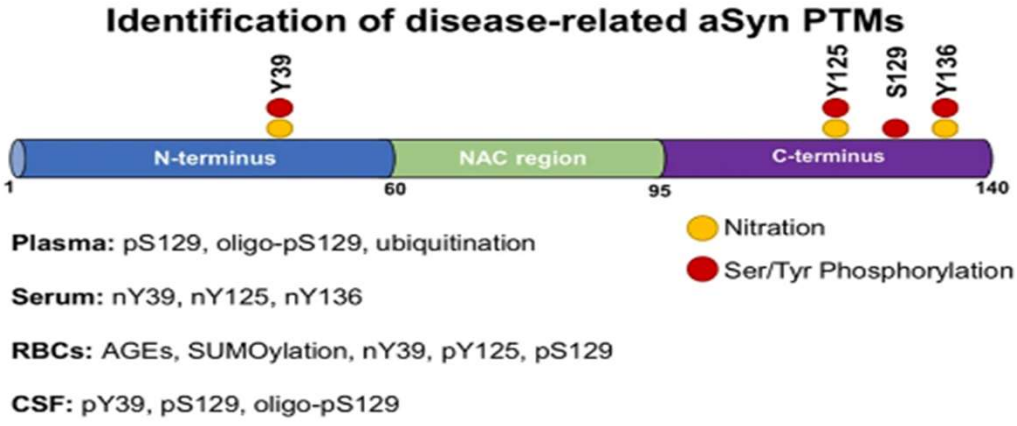
nature › npj parkinson's disease › review articles › article

Review Article | Open Access | Published: 22 July 2022

Opportunities and challenges of alpha-synuclein as a potential biomarker for Parkinson's disease and other synucleinopathies

Pedro Magalhães & Hilal A. Lashuel

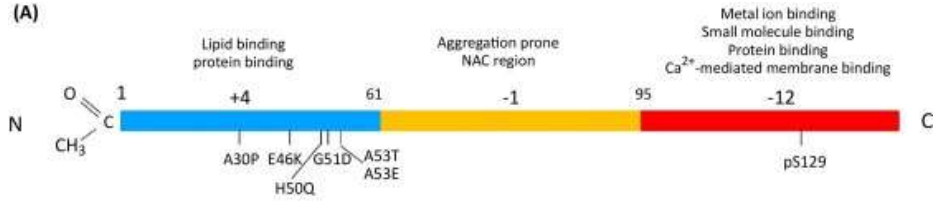
npj Parkinson's Disease **8**, Article number: 93 (2022) | Cite this article



Magalhães et al., 2022

α-Synuclein
Function - pS129-α-syn

PTM of **α**-syn in LB is 90% is phosphorylated pS129-**α**-syn (4% in normal)



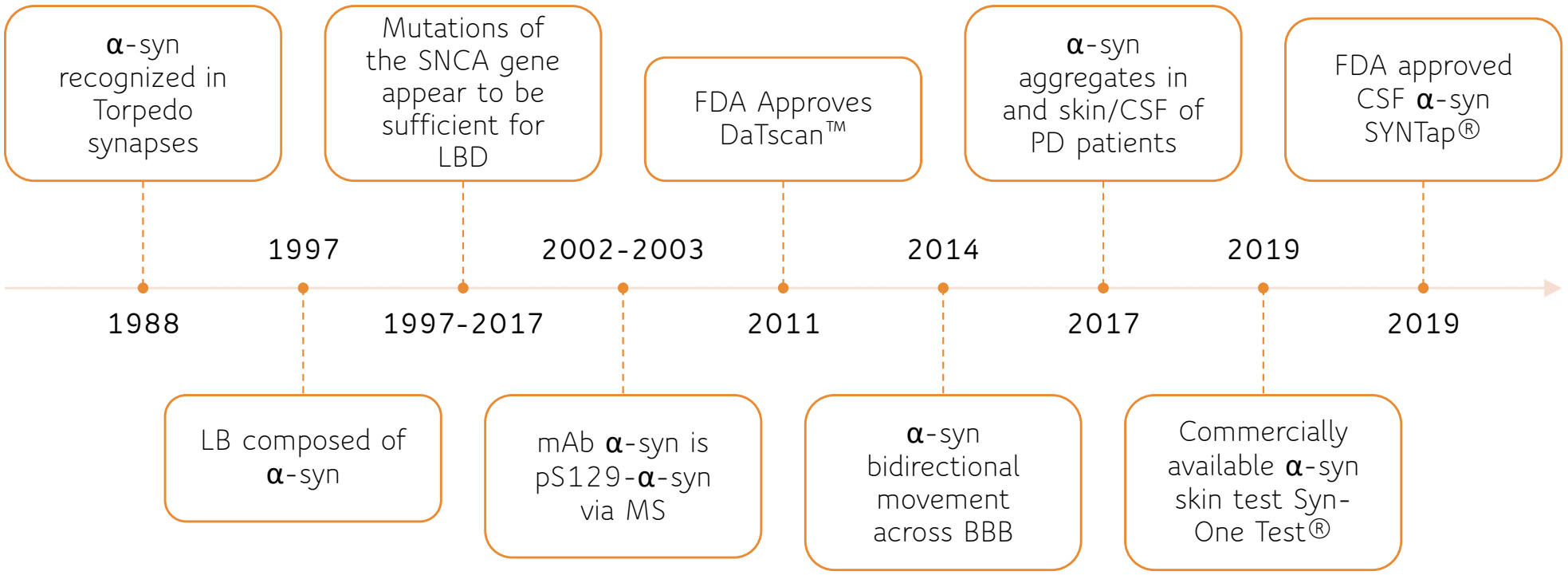
pS129-**α**-syn are as a regulator of dopamine uptake

- pS129-**α**-syn increases expression of DAT at terminal
- pS129-**α**-syn inhibits the binding of **α**-syn oligomers at terminal indirectly decreases **α**-syn oligomer induced pore formation

pS129-**α**-syn is early Cytoprotective but Late Cytotoxic?

Anderson et al., 2006; Bernal-Conde et al., 2020

α-Synuclein
History



Spillantini et al., 1997; Braak et al., 2004; Kosaka et al., 2013; Wang et al., 2020

α-Synuclein
Biomarkers – Positron Emission Topography

SPECT-DaTscan™

- Tracers specific to dopamine transporters and dihydroxyphenylalanine activity
- Differentiate DDA vs non-DDA diseases SEN/SPE 85/80%
- 10% autopsy proven DLB have normal DaTscan
- Change in care management >50% cases/ Altered diagnosis >30% cases

PET-α-syn – >10 years of research, **no compound yet**

- Two compounds have high sensitivity to α-syn fibrils
  - [11C]MODAG-001 [125I]TZ6184
- Four compounds have high selectivity (30-50x) vs. Aβ and tau fibrils
  - [18F]2FBox, [18F]15a, [11C]MODAG-001, [18F]S3-1
- <u>No current valid candidate for **α**-syn PET due to lack of reliable and reproducible assays.</u>

^{123}I-FP-CIT (DaTscan™) **FDA approved 2011*

^{18}F-AV-133 (Investigational use)


nature › npj parkinson's disease › review articles › article

Review Article | Open Access | Published: 24 May 2021

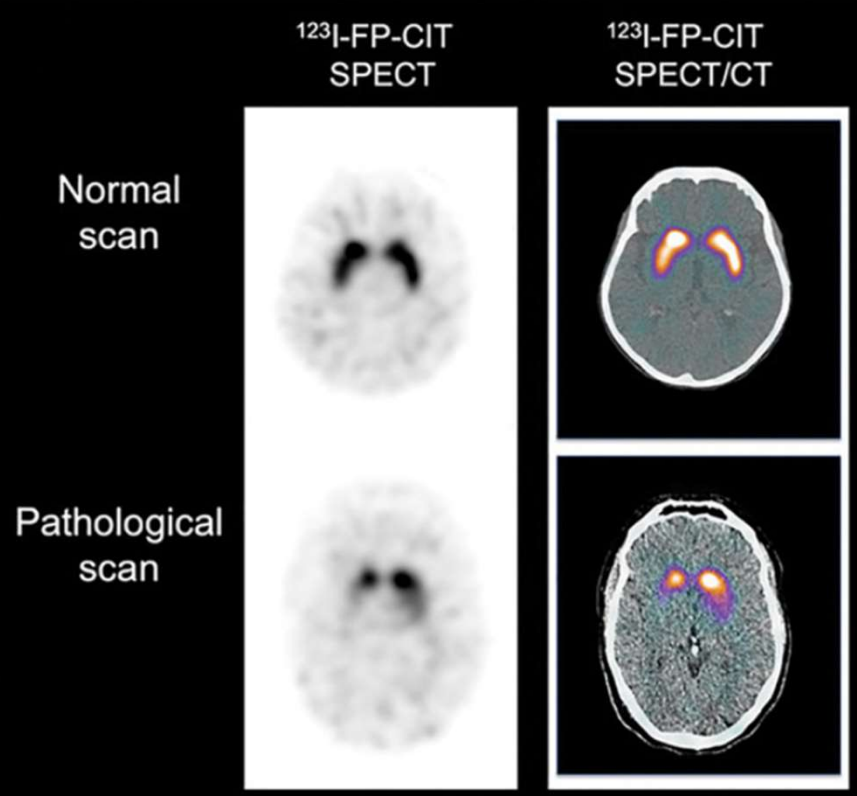
Clinical utility of DaTscan in patients with suspected Parkinsonian syndrome: a systematic review and meta-analysis

Danny Bega, Phillip H. Kuo, Anastasia Chalkidou, Mariusz T. Grzeda, Thomas Macmillan, Christine Brand, Zulfiqar H. Sheikh & Angelo Antonini

npj Parkinson's Disease 7, Article number: 43 (2021) | Cite this article

dopamine deficiency aetiologies (non-DDA)

Calabria et al., 2016; Meyer et al., 2017; Ganguly et al., 2021; Bega et al., 2021; Korat et al., 2021

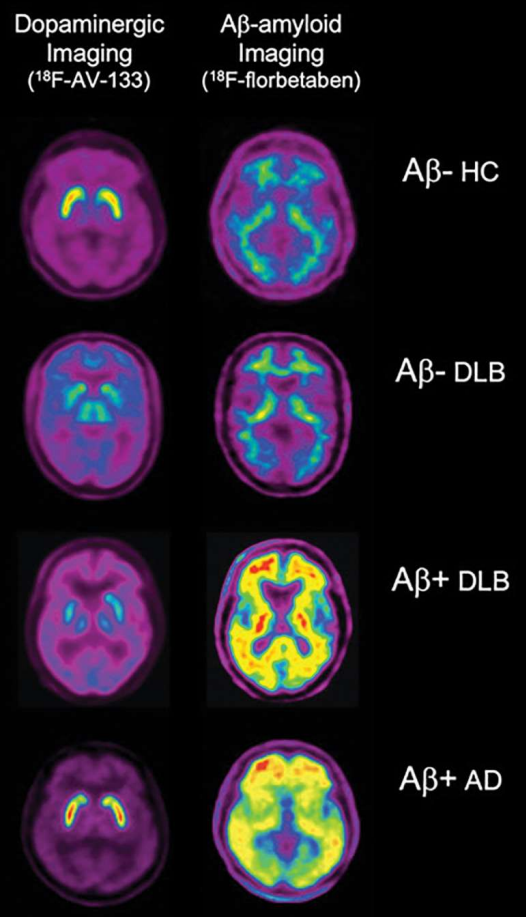


dopamine deficiency degeneration (PD/DLB) appears as asymmetric/decrease of tracer binding in striatum

DLB = AD with Aβ-PET

Reduced VMAT2 densities in striatum, clearly differentiating DLB vs HC/AD.

Vesicular monoamine transporter type 2 (VMAT2)
^{18}F-AV-133 imaging



Villemagne et al., 2021

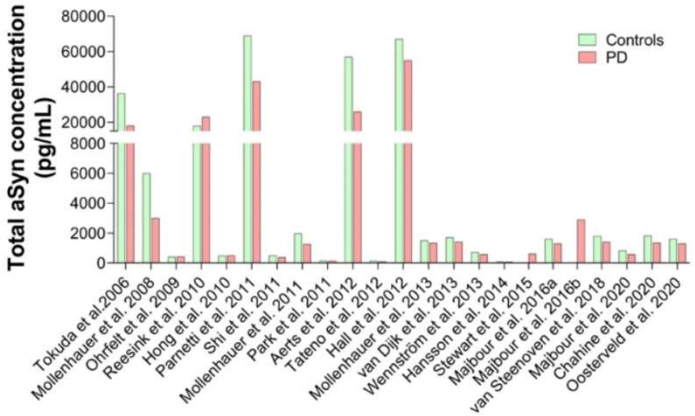
α-Synuclein
Biomarkers - Cerebrospinal Fluid

Total α-syn via ELISA
- Lower total α-syn in CSF between PD and NC, but results are inconsistent with low specificity
- Combination o-α-syn/total α-syn improved low specificity

α-syn protofibrils (PFs) via SIMOA
- Elevated α-syn PFs in PD vs NC

pS129 α-syn via IM/MS
- Higher pS129/total α-syn in PD vs HC or PSP
- Low correlation with PD severity

α-syn-PMCA assay
- High sensitivity/specificity o-α-syn in CSF between PD and HC/MSA
- SEN/SPE 93.6/100%



Article | Published: 05 February 2020

Discriminating α-synuclein strains in Parkinson's disease and multiple system atrophy

Mohammad Shahnawaz, Abhisek Mukherjee, Sandra Pritzkow, Nicolas Mendez, Prakruti Rabadia, Xiangan Liu, Bo Hu, Ann Schmeichel, Wolfgang Singer, Gang Wu, Ah-Lim Tsai, Hamid Shirani, K. Peter R. Nilsson, Phillip A. Low & Claudio Soto

Nature **578**, 273–277 (2020) | Cite this article

Protein Misfolding Cyclic Amplification (PMCA) (also α-syn-RT-QuIC)

Wang Y. et al., 2012; Shahnawaz et al., 2017, Shahnawaz et al., 2020; Chahine et al., 2020; von Euler Chelpin et al., 2020; Ganguly et al., 2021; Magalhães et al., 2022

α-Synuclein
Biomarkers – Plasma

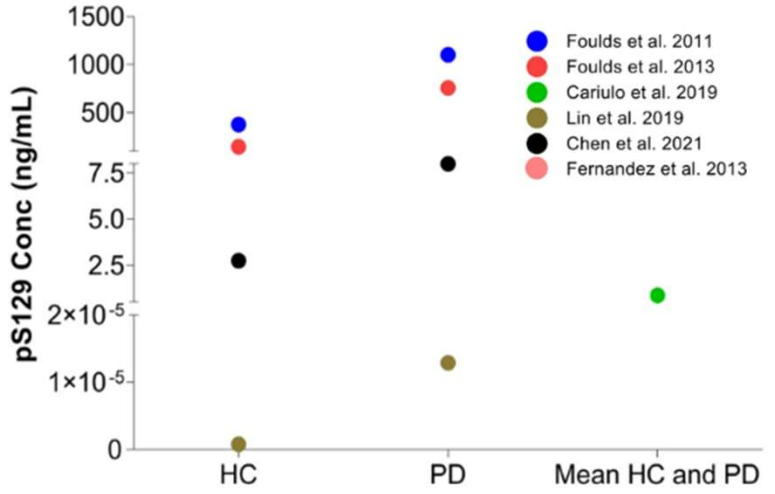
Plasma

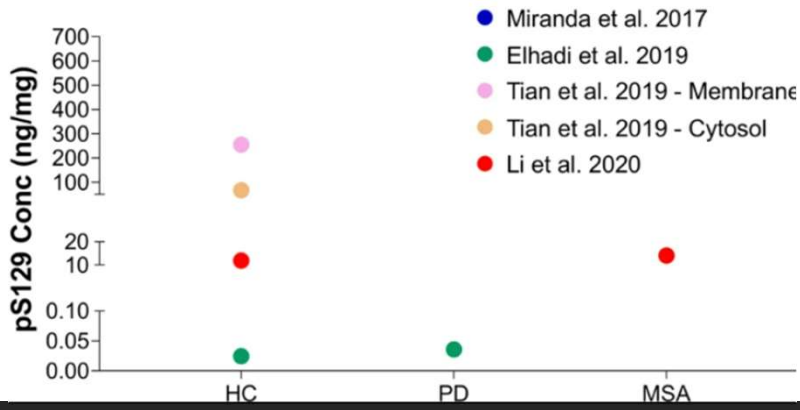
- Total α-syn via ELISA
  - Variable and inconsistent
- pS129 α-syn
  - Elevated in PD vs HC via ELISA
  - Elevated in PD vs HC via IM/MS

RBCs are major source of aSyn in the plasma

- Elevated α-syn in RBC vs Plasma
- Elevated pS129 α-syn PD/MSA vs HC via IM/MS
- Elevated pS129 α-syn MSA-P vs MSA-C via IM/MS

Cohorts remain small, no commercially available testing





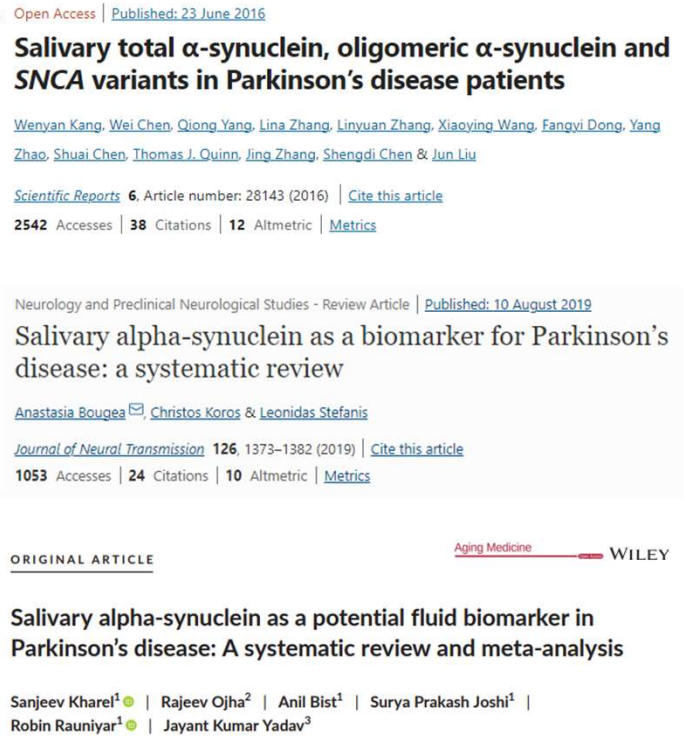
Chahine et al., 2020; von Euler Chelpin et al., 2020; Ganguly et al., 2021; Magalhães et al., 2022

α-Synuclein
Biomarkers – Saliva

Saliva α-syn
- Decrease total α-syn of PD vs. HC
- Increase in o-α-syn and o-α-syn/total α-syn in PD vs. HC
- Total α-syn decreased with age
- Total α-syn no correlation with disease duration or severity

2019 meta-analysis (8 studies)
- salivary o-α-syn is promising
- salivary total α-synuclein is not

2022 meta-analysis (13 studies)
- salivary α-syn simple, easy-to-use, cost-effective, and reliable
- salivary α-syn (total, oligomeric, oligo/total) *all* promising



Open Access | Published: 23 June 2016

Salivary total α-synuclein, oligomeric α-synuclein and *SNCA* variants in Parkinson's disease patients

Wenyan Kang, Wei Chen, Qiong Yang, Lina Zhang, Linyuan Zhang, Xiaoying Wang, Fangyi Dong, Yang Zhao, Shuai Chen, Thomas J. Quinn, Jing Zhang, Shengdi Chen & Jun Liu

Scientific Reports **6**, Article number: 28143 (2016) | Cite this article

2542 Accesses | **38** Citations | **12** Altmetric | Metrics

Neurology and Preclinical Neurological Studies - Review Article | Published: 10 August 2019

Salivary alpha-synuclein as a biomarker for Parkinson's disease: a systematic review

Anastasia Bougea, Christos Koros & Leonidas Stefanis

Journal of Neural Transmission **126**, 1373–1382 (2019) | Cite this article

1053 Accesses | **24** Citations | **10** Altmetric | Metrics

ORIGINAL ARTICLE

Aging Medicine — WILEY

Salivary alpha-synuclein as a potential fluid biomarker in Parkinson's disease: A systematic review and meta-analysis

Sanjeev Kharel[1] | Rajeev Ojha[2] | Anil Bist[1] | Surya Prakash Joshi[1] | Robin Rauniyar[1] | Jayant Kumar Yadav[3]

Devic et al., 2011; Al-Nimer et al., 2014. Kang et al., 2016; Bougea et al., 2019; Shaheen et al. 2020; Kharel et al., 2022

α-Synuclein
Biomarkers – Skin

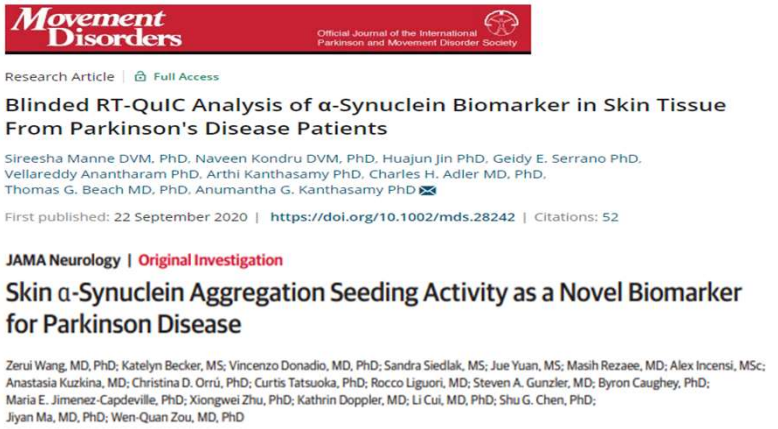
Author	Date	HC	ADNLB	Autopsy LBD	Clinical LBD	SEN	SPE
Ikemura et al.	2008	194		142		40-70	100
Beach et al.	2010	23	17	40			100
Wang et al.	2013	14			20	100	
Donadio et al.,	2013	15	12		9	100	100
Gelpi et al.	2014	13		15			100
Doppler et al.	2014				31	52	100
Donadio et al.,	2014	30			41	100	100
Rodríguez-Leyva et al.	2014	17	10		17		
Doppler et al.	2015	39	15		42	73-75	100
Zange et al.,	2015		6		20		100
Gibbons et al.	2016	23			28	>90	>90
Donadio et al.,	2016	15			30	100	
Gibbons et al.	2017	5		11		100	100
Donadio et al.,	2017	25	23		18	100	100

PD (punch biopsy x 2)

- sensitivity/specificity 95%/100% for RT-QuIC
- sensitivity/specificity 80%/90% for PMCA

CND LifeScience Syn-One® **not approved by FDA

- Fluorescent immunostaining Punch-biopsy x3


Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

Research Article | Full Access

Blinded RT-QuIC Analysis of α-Synuclein Biomarker in Skin Tissue From Parkinson's Disease Patients

Sireesha Manne DVM, PhD, Naveen Kondru DVM, PhD, Huajun Jin PhD, Geidy E. Serrano PhD, Vellareddy Anantharam PhD, Arthi Kanthasamy PhD, Charles H. Adler MD, PhD, Thomas G. Beach MD, PhD, Anumantha G. Kanthasamy PhD

First published: 22 September 2020 | https://doi.org/10.1002/mds.28242 | Citations: 52

JAMA Neurology | Original Investigation

Skin α-Synuclein Aggregation Seeding Activity as a Novel Biomarker for Parkinson Disease

Zerui Wang, MD, PhD; Katelyn Becker, MS; Vincenzo Donadio, MD, PhD; Sandra Siedlak, MS; Jue Yuan, MS; Masih Rezaee, MD; Alex Incensi, MSc; Anastasia Kuzkina, MD; Christina D. Orrú, PhD; Curtis Tatsuoka, PhD; Rocco Liguori, MD; Steven A. Gunzler, MD; Byron Caughey, PhD; Maria E. Jimenez-Capdeville, PhD; Xiongwei Zhu, PhD; Kathrin Doppler, MD; Li Cui, MD, PhD; Shu G. Chen, PhD; Jiyan Ma, MD, PhD; Wen-Quan Zou, MD, PhD

Fluorescent immunostaining (FI)
Real-time quaking-induced conversiamplificationon (RT-QuIC)
Protein Misfolding Cyclic Amplification (PMCA) (also **α**-syn-RT-QuIC)

Ikemura et al. 2008; Wang et al., 2013; Provitera et al., 2016; Gibbons et al., 2016; Kim et al., 2019; Manne et al., 2020; Wang et al., 2020

α-Synuclein
Take away points

α-syn is a small, disorganized impetuous protein that goes everywhere and causes trouble if untethered

Unclear if α-syn is cause of synucleinopathies, but at minimum is a necessary step

pS129-α-syn at the center of the problem

- DaTscan™ are expensive
- Amprion SYNTap® - Invasive but very sensitive/specific
- CND LifeScience Syn-One® - Questionably sensitive, but very specific

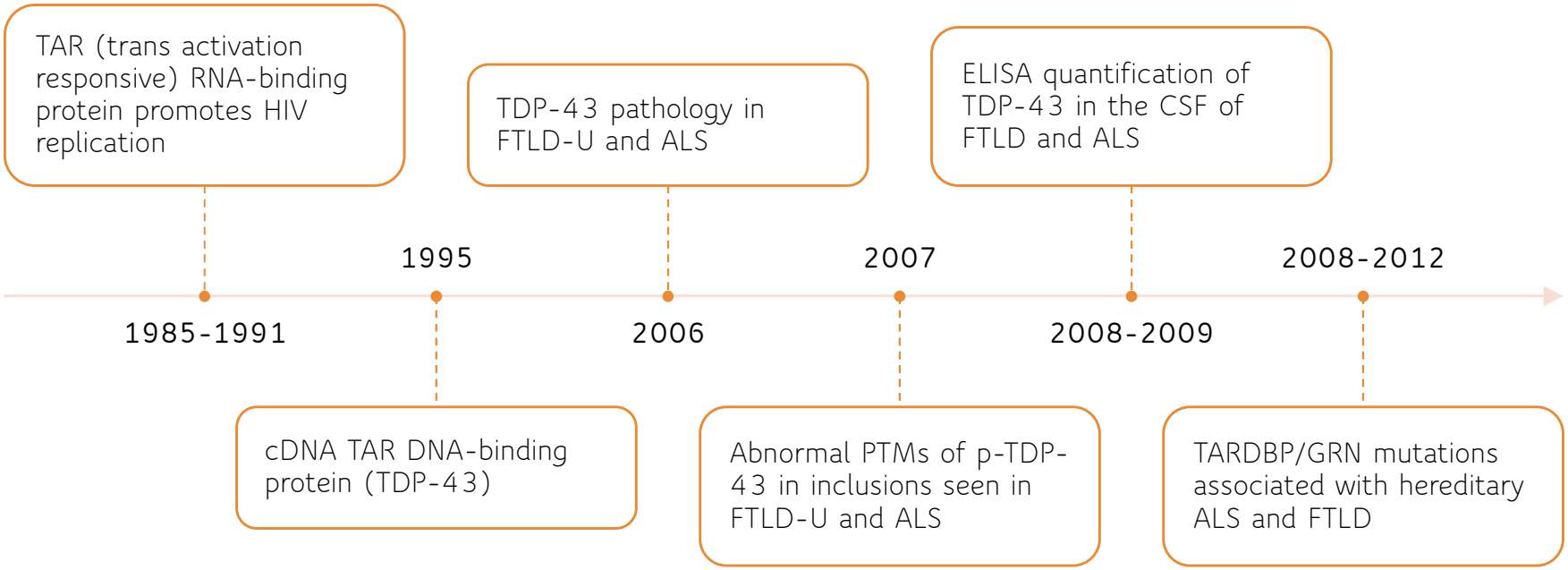
pS129-α-syn is NECESSARY but *unlikely* SUFFICIENT

TDP43

TAR DNA-BINDING PROTEIN 43

TAR DNA-binding Protein 43 (TDP43)

History



Rosen et al., 1985; Gatignol et al., 1991; Rosen et al., 1995; Neumann et al., 2006; Hasegawa et al. 2008; Foulds et al., 2008; Kasai et al., 2009

TAR DNA-binding Protein 43 (TDP43)
Function

Common to ALS, FTLD, AD, LATE

Highly conserved nuclear heterogeneous nuclear ribonucleoprotein (hnRNP) encoded by the TARDP on chromosome 1

Similar to α-synuclein

- *DISORGANIZED* – IDP and soluble
- *PRION-ish* - Prion-like properties
- PTMs associated with aggregation

Many important functions including modulating splicing activity, chaperoning proteins, and self-regulatory transcriptional function

*Intrinsically disordered proteins (IDP)

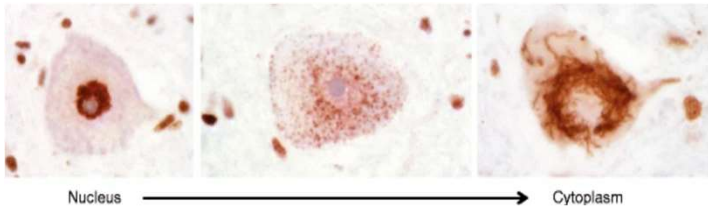
Jo et al.,2020

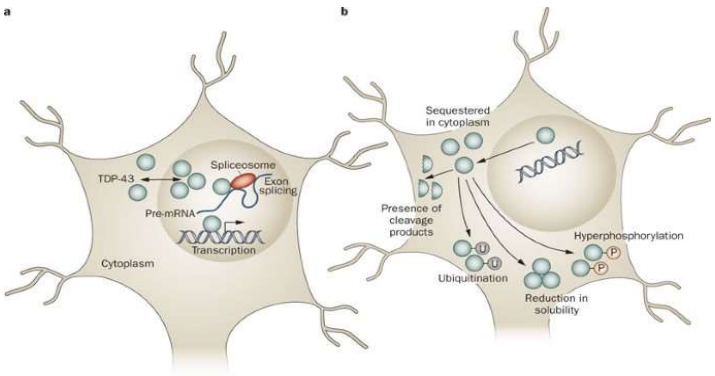
TAR DNA-binding Protein 43 (TDP43)
Function

Physiological conditions
- TDP-43 is a mainly nuclear protein
- Under physiological **stress** TDP-43 accumulates in cytoplasm to form SGs
- Regulated via a negative-feedback

Pathological (AL/FTLD) conditions,
- Chronic physiological stress prolongs SG formation, which leads to persistent accumulation of cytoplasmic TDP-43 aggregates

Both loss of function and toxic gain of function are associated with mis-localization, aggregation, and inclusions
- Pathological inclusions contain pS403/4-TDP-43 and pS409/10-TDP-43
- pTDP43 misfolds and propagated to other cells through unknown mechanisms





stress granules (SGs)

Chen-Plotkin et al., 2010; Jo et al.,2020

TAR DNA-binding Protein 43 (TDP43)
Biomarkers

No fluid-based assays specific for pathological forms of the protein

No imaging specific for pathological forms of the protein

Wide range of TDP-43 mAb used to detect TDP-43 in biofluids

- Available commercial mAb are restricted - bind to AA 1-260, 205-222, or 256-296
- mAb often MISS disease-specific truncated forms of TDP-43 in biofluids

HIGH variability between trials in ability discriminate ALS/FTLD

Jo et al.,2020

TAR DNA-binding Protein 43 (TDP43)

Biomarkers - CSF

Limited capacity for stratification of FTLD-tau vs. FTLD-TDP using CSF p-tau, p-tau/total tau

2018 Meta-analysis (7 studies)

- CSF TDP-43 tends to be significantly increased in patients with FTD-ALS spectrum, but NOT FTLD

Majumder *et al. BMC Neurology* (2018) 18:90
https://doi.org/10.1186/s12883-018-1091-7

BMC Neurology

RESEARCH ARTICLE Open Access

TDP-43 as a potential biomarker for amyotrophic lateral sclerosis: a systematic review and meta-analysis

Vivek Majumder[1†], Jenna M. Gregory[1,2*†], Marcelo A. Barria[3], Alison Green[3] and Suvankar Pal[1,2,3*]

Majumder et al., 2018; Jo et al.,2020

TAR DNA-binding Protein 43 (TDP43)

Biomarkers - Plasma

Plasma TDP43 discriminates ALS from HC

- Increase Plasma TDP-43 and pTDP-43
- Decrease Plasma pTDP-43/TDP-43 ratios
- AUC 0.924 SEN/SEP 91.3%/91.5%

Plasma TDP43 not diagnostic yet for FTLD-TDP43

TDP-43 and Phosphorylated TDP-43 Levels in Paired Plasma and CSF Samples in Amyotrophic Lateral Sclerosis

Yuting Ren[1,2], Siyuan Li[1], Siyu Chen[3], Xiaosun Sun[1,4], Fei Yang[1], Hongfen Wang[1], Mao Li[1], Fang Cui[1] and Xusheng Huang[1]*

Ren et al., 2021; Cousins et al., 2022

TAR DNA-binding Protein 43 (TDP43)

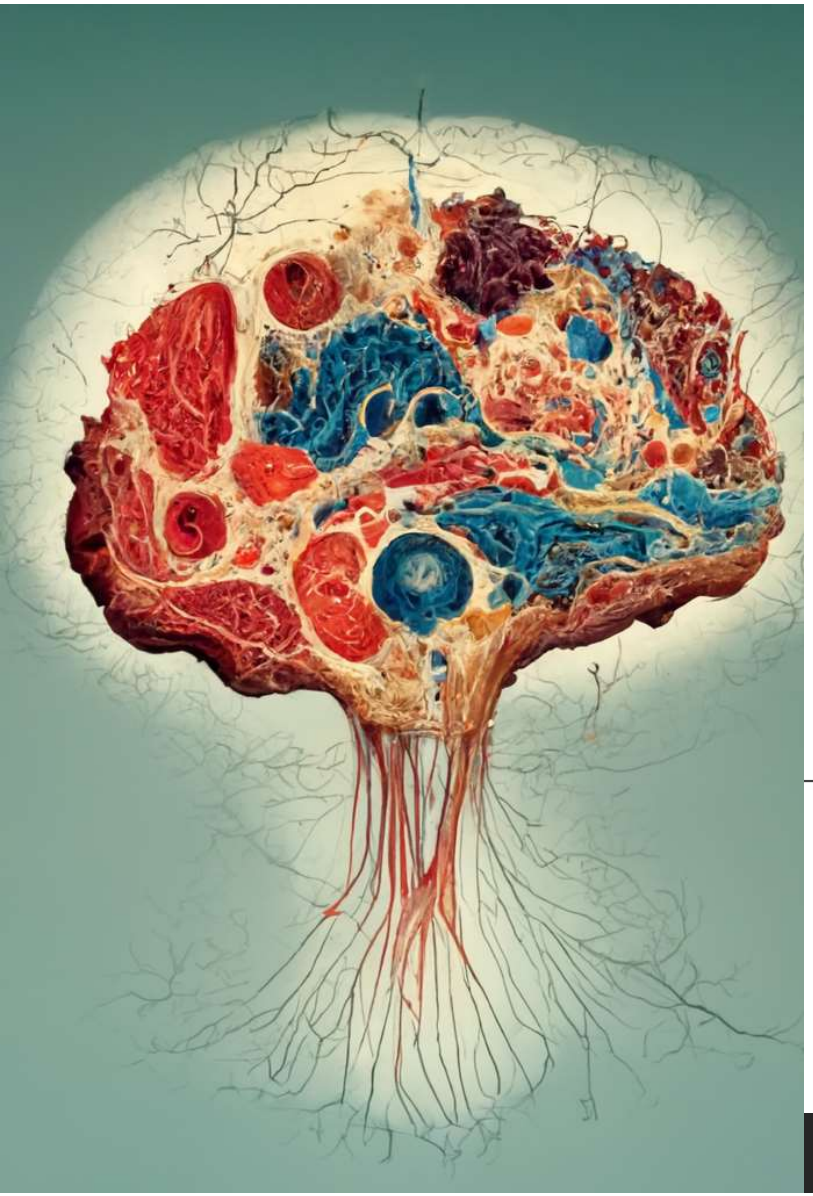
Take away points

No fluid-based assays specific for pathological forms of the protein in FTLD.

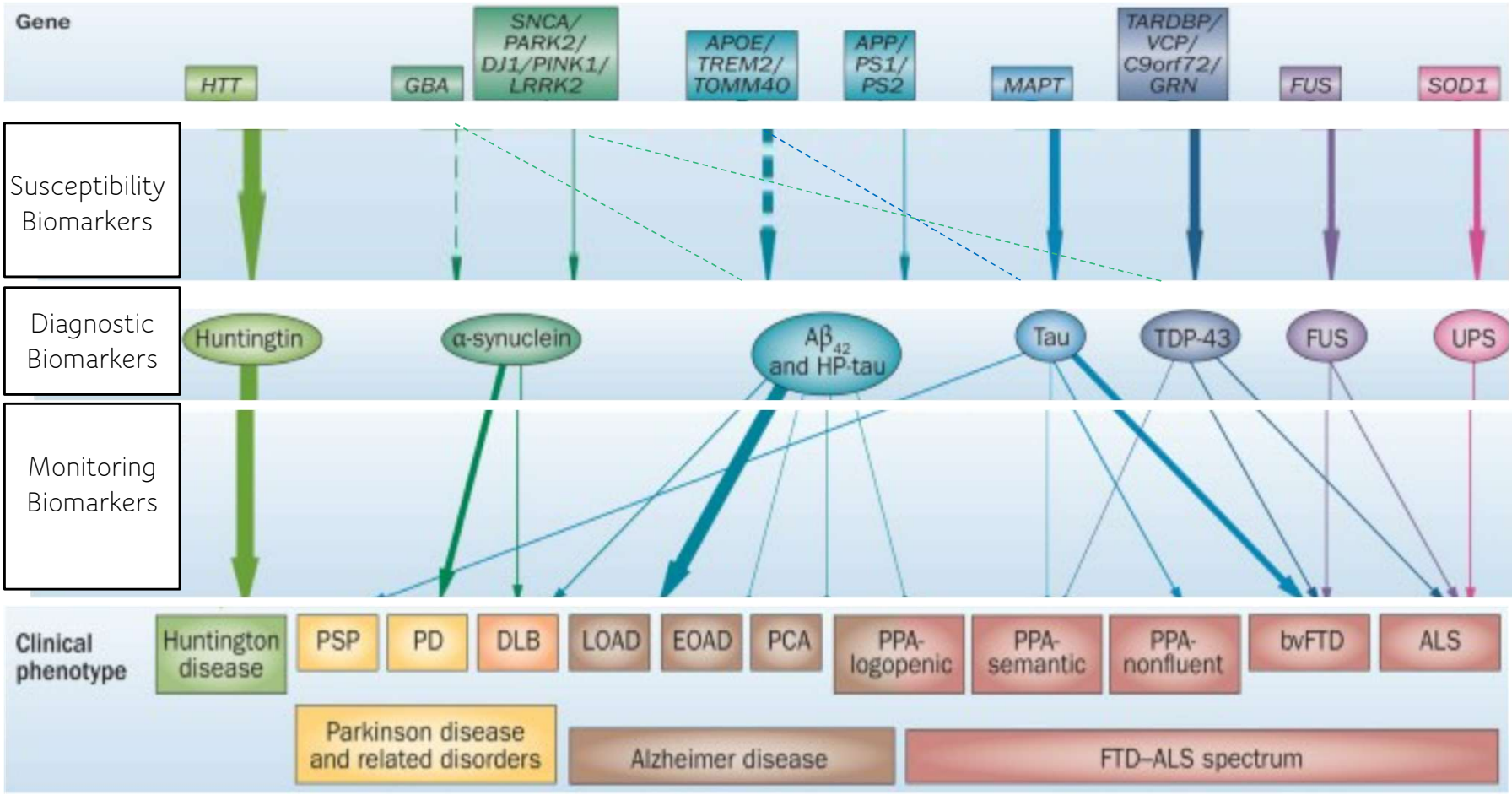
No imaging specific for pathological forms of the protein.

Promising plasma biomarker for ALS

- ALS associated with Increase Plasma TDP-43, pTDP-43
- ALS associated with Decrease pTDP-43/TDP-43 ratio



Surrogate Biomarkers



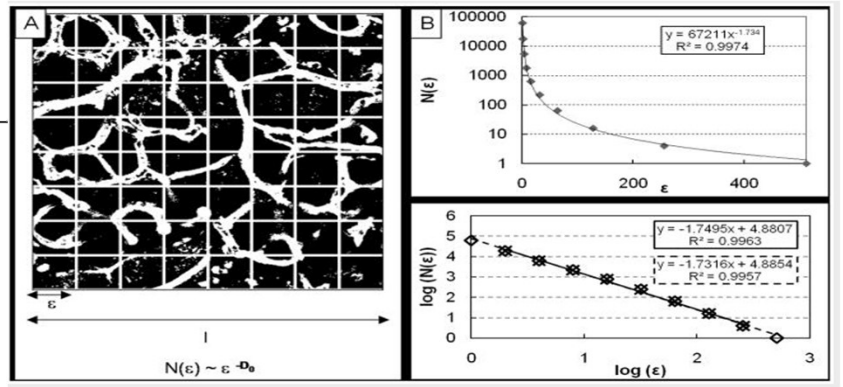
Pievani et al., 2014; Gan et al., 2018

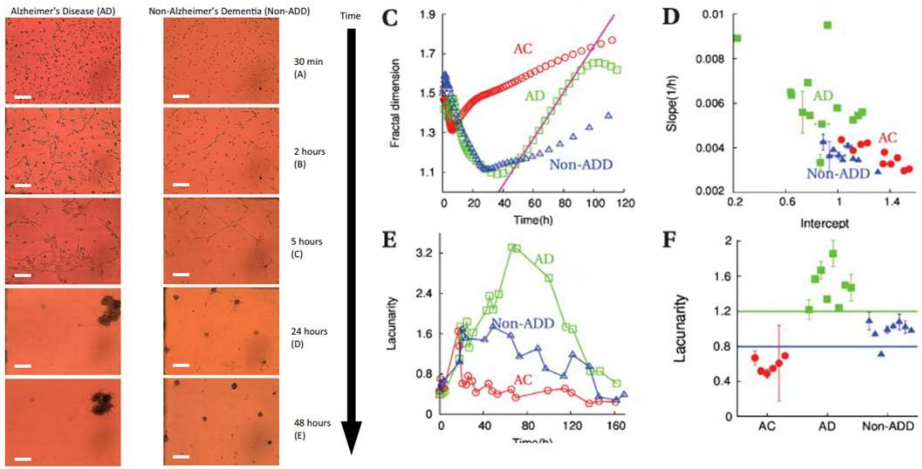
Fibroblast Changes
Biomarkers – Skin

- CNS ADRP has PNS tissue correlates like in PD

- Fibroblasts have a complex interconnected network-like structure as measured by spatiotemporal fractal lacunarity.
  - Autopsy proven AD/Mixed AD vs HC/non-AD fibroblast in culture treated with oligomerized Aβ showed a steeper loss of fractal complexity

Vascular/fibroblast growth can be described in terms of mean diameter of vessels, mean length of vessel segments, branch angle, vessel area density i.e fraction area occupied and length density





Gould et al., 2011; Chirila et al., 2012; Chirila et al., 2022

Fibroblast Changes
Biomarkers – Skin

- NeuroDiagnostics DISCERN™
  - FDA approved 2018
  - Medicare covered (206U/207U) 2021
- Liquid Punch Biopsy
  - Morphometric Imaging (MI) – per their own studies SEN/SPE 95/95% for autopsy AD/Mixed AD vs NC/non-AD
  - PKCε Assay – complement to MI (small studies claim SEN/SPE 100/96%)
  - Phosphorylated Erk1 and Erk2 – complement to MI
- Limitations
  - No longitudinal studies
  - No staging studies
  - No clinical correlations studies

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scientific reports

Check for updates

OPEN

Morphometric imaging biomarker identifies Alzheimer's disease even among mixed dementia patients

Florin V. Chirila[1,2], Guang Xu[1], Dan Fontaine[1], Grant Kern[1], Tapan K. Khan[1], Jason Brandt[3], Yoshihiro Konishi[4], Gerhard Nebe-von-Caron[5], Charles L. White III[6] & Daniel L. Alkon[1]✉

Khan et al., 2006; Chirila et al., 2013; Chirila et al., 2014; Khan et al., 2014; Khan et al., 2015; Chirila et al., 2022

NOS Markers Neurodegeneraton

Neuronal injury

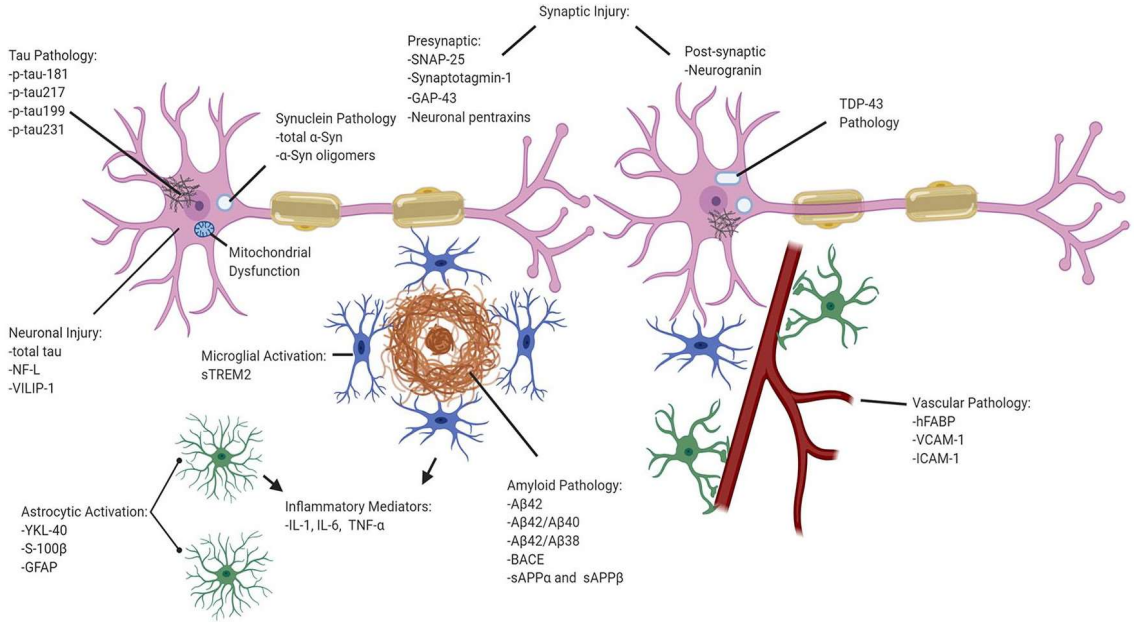
- Neurofilament light chain, VILIP-1

Synaptic integrity/function

- Neurogranin, Synaptobrevin, Synaptotagmin, Syntaxin, SNAP-25, SCG2, PDYN, GAP-43

Glial (astrocytic/microglia) proteins

- Glial fibrillary acidic protein (GFAP), YKL-40 (chitinase-3-like-1 protein), S100 calcium-binding protein B (S100B), TREM2



Tarawneh et al .2020

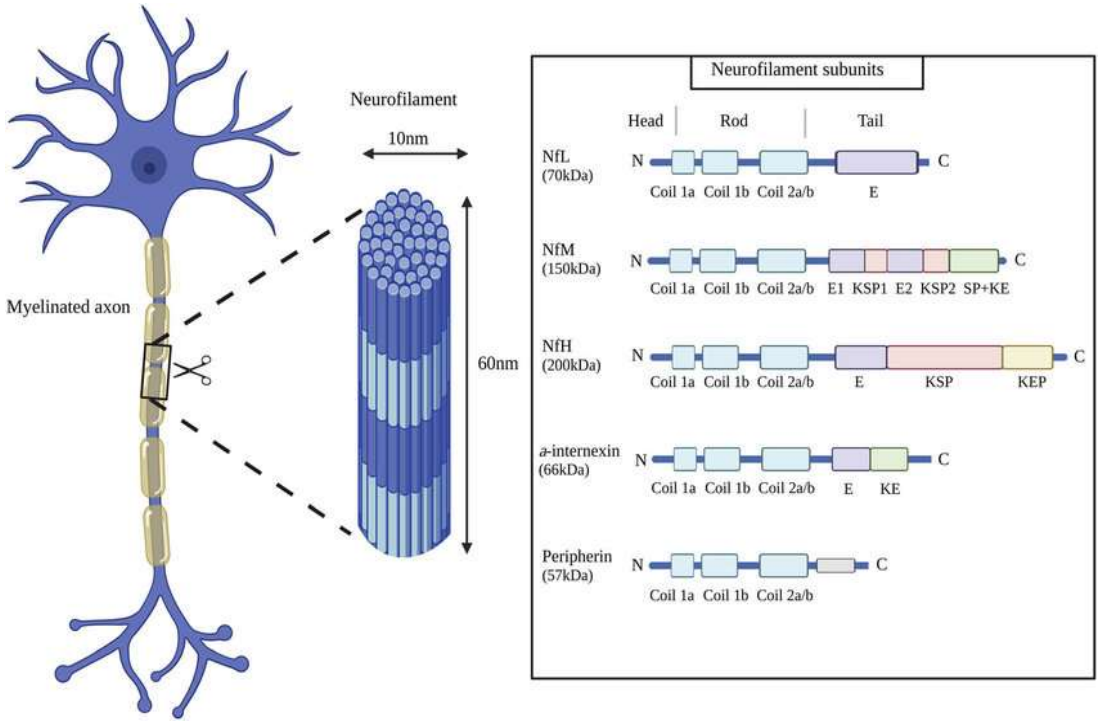
Neurofilament Light Chain

Neurofilaments are neuronal-specific heteropolymers in NS

- Triplet of heavy, medium, and light chain (NfL)
- α-Internexin in CNS
- peripherin in PNS

Most abundant protein in myelinated axons

Stable for months to years



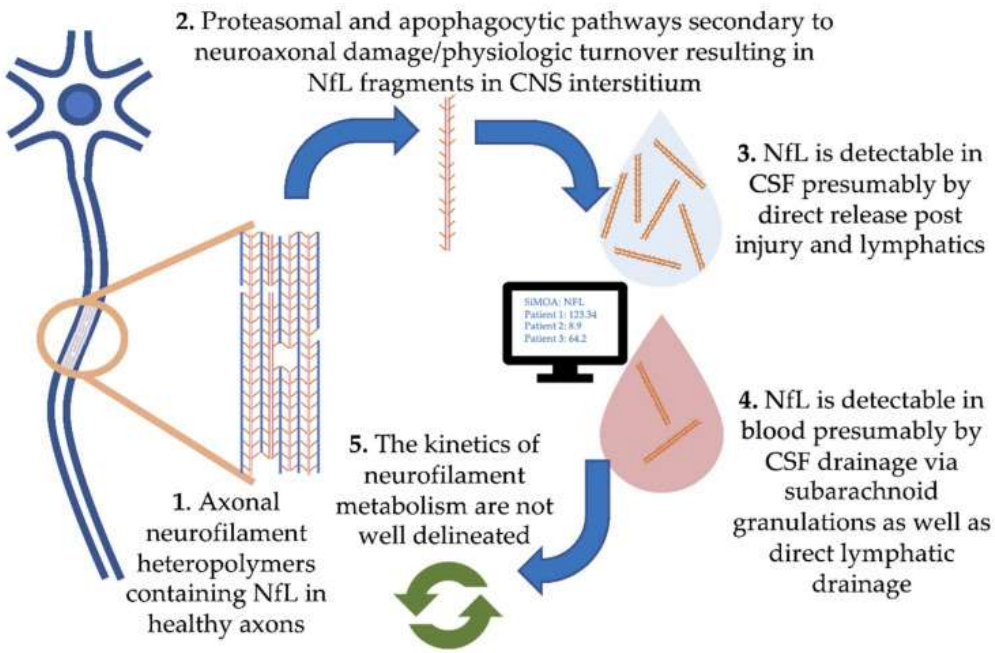
Thebault et al., 2020

Neurofilament Light Chain

NfL is neuron-specific marker of neurological injury

- Intrathecal catheter insertion
  - Peaked 1-month post-surgery
  - Baseline 6-9 months post-surgery
- MS relapse
  - Increasing 5 months before
  - Peak clinical onset
  - Recovery 4-5 month after

NOT specific for neurodegeneration



Thebault et al., 2020

Neurofilament Light Chain

Neurodegenerative Disease

RELATIVE to healthy controls

- Plasma and CSF Nfl have similar effect sizes
- Elevated plasma NfL is a prognostic marker of degeneration on MRI
- Elevated plasma NfL is a prognostic marker of cognitive impairment

Due to **LACK of specificity**, diagnostic utility is limited

- Positive NfL in Autosomal dominant ADD in 30s well before SXS onset
- Positive NfL in PD in 70s long after disability onset

Budelier & Bateman, 2020; Mielke et al., 2021

Neurofilament Light Chain

Neuroimaging

Strongly associated with

- White matter integrity as assessed by DTI/FA and WMH
- Longitudinal cingulum/Corpus callosum independent of amyloid pathology

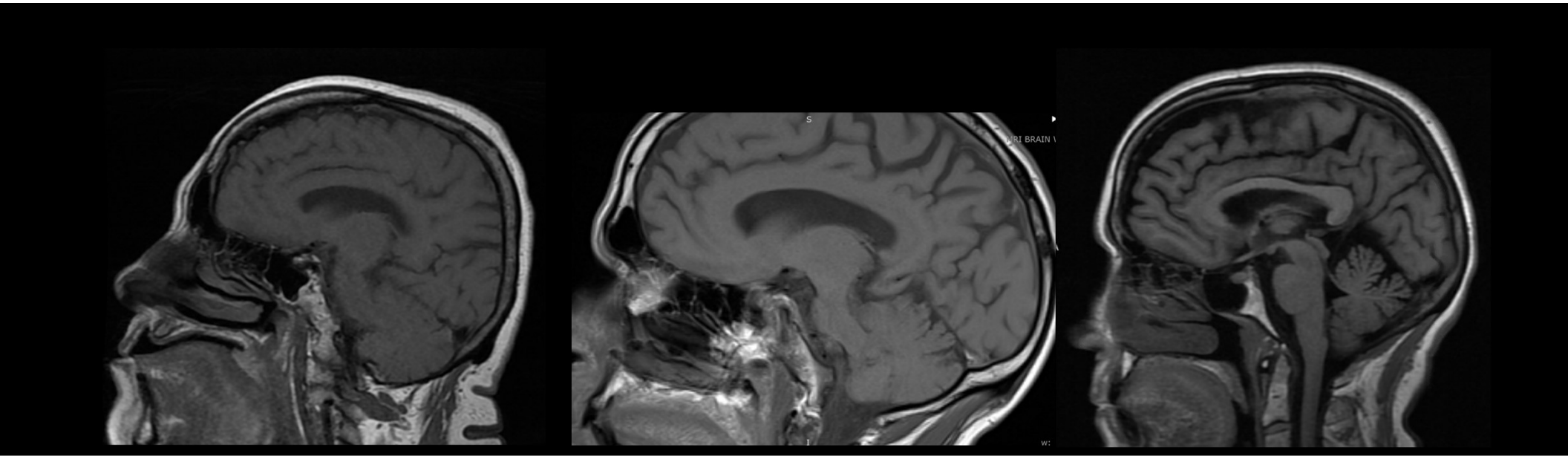
Modestly associated with

- Hippocampal atrophy independent of amyloid pathology

NOT associated with

- Cortical thickness

Budelier & Bateman, 2020; Mielke et al., 2021



77 y/o SCI
*MDD + severe medical multiple stressors in last 6 months

Neurofilament Light Chain, P	38.9	h	pg/mL	<=37.9

64 y/o early-onset Alzheimer's disease
*clinical stable for last 12-months

Neurofilament Light Chain, P	15.5		pg/mL	<=28.0

Abeta42	>1026 pg/mL	790 ⌄
Total-Tau	<=238 pg/mL	289 ^
Phospho-Tau(181P)	<=21.7 pg/mL	33.6 ^

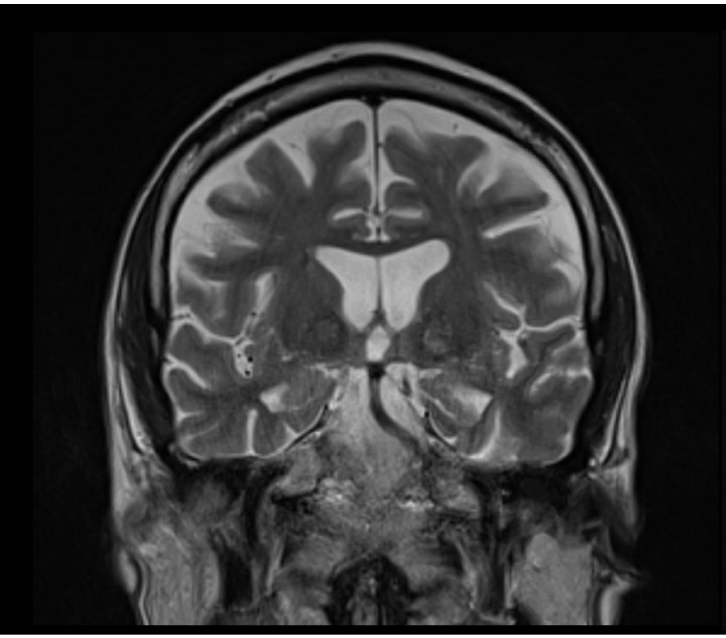
63 y/o early-onset Alzheimer's disease
*very slow course MCI after 5-years

Neurofilament Light Chain, P	16.1		pg/mL	<=28.0

Abeta42	616	l	pg/mL	>1026
Total-Tau	313	h	pg/mL	<=238
Phospho-Tau(181P)	29.2	h	pg/mL	<=21.7

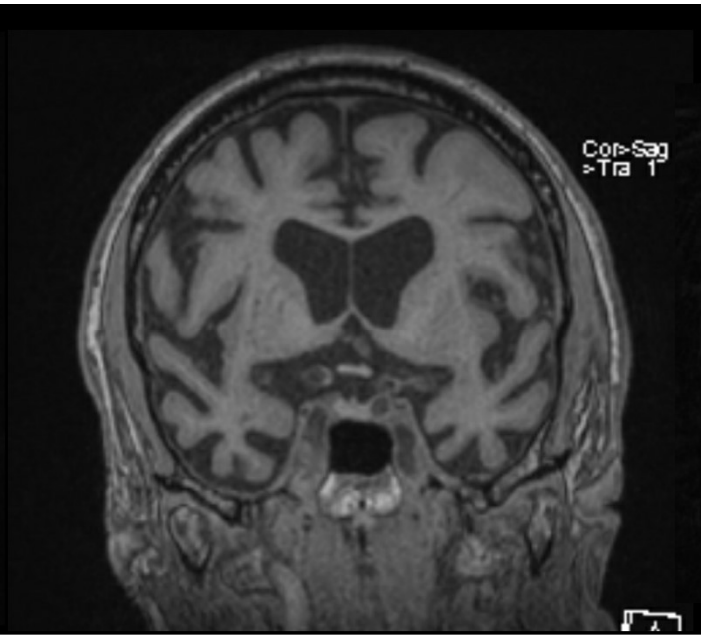
*Nfl drawn same time as AD biomarkers

Possible association with stressor/neuroinflammation but not chronic degeneration?



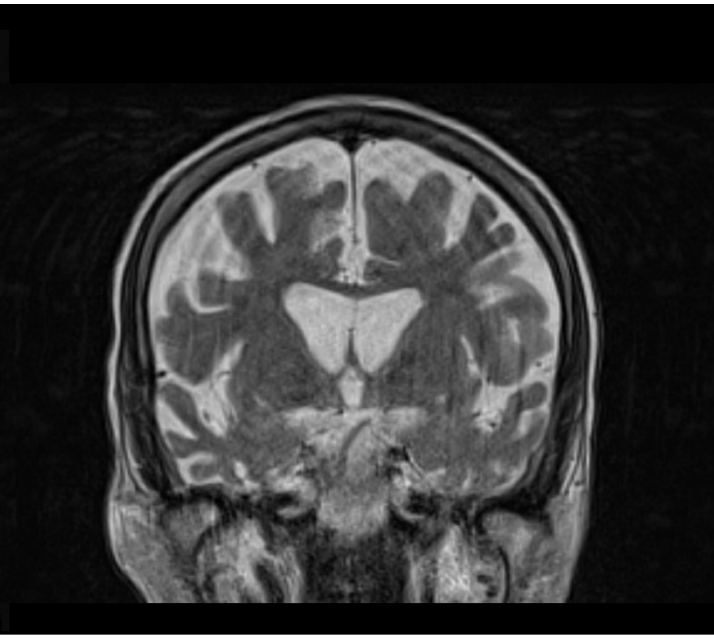
66 y/o MCI with bvFTD phenotype
*severe baseline neuropsychiatric SXS
*prolonged SXS >5 years

Neurofilament Light Chain, P 12.5 pg/mL <=28.0



78 y/o bvFTD likely mixed pathology
*stable R-TLE
*stable SXS for last year

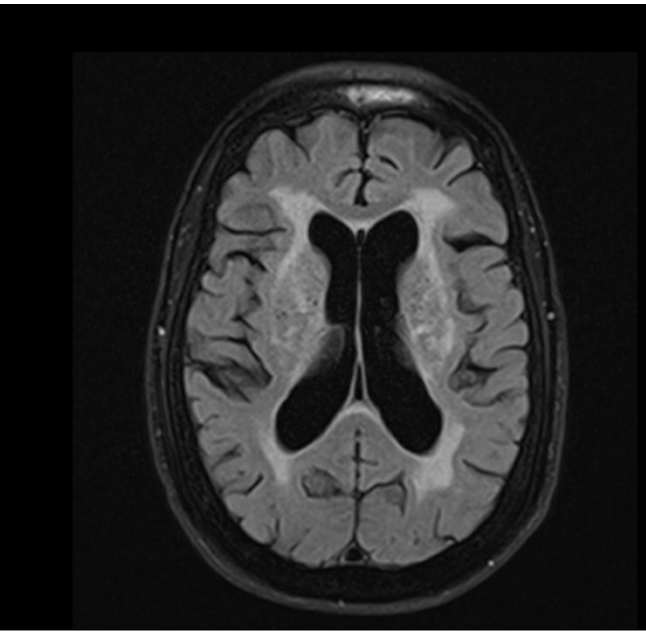
Neurofilament Light Chain, P 13.9 pg/mL <=37.9



77 y/o bvFTD with semantic aphasia
*relatively quick decline <2 years

Neurofilament Light Chain, P 34.9 pg/mL <=37.9

Does not really distinguish between psych and bvFTD….



80 y/o MCI with leukoencephalopathy
*Recurrent neurocardiogenic syncope
2/2 psoriasis DMTs

Neurofilament Light Chain, P 60.9 h pg/mL <=37.9

84 y/o prodromal mixed-dementia
*ESRD on HD

Neurofilament Light Chain, P 269 h pg/mL <=51.2

77 y/o mixed-dementia
*Recent decompensation 6 months
MDS/chronic hyponatremia

Neurofilament Light Chain, P 89.3 h pg/mL <=37.9

Does correlate with microvascular disease burden, ESRD, and recent decompensation….


"What I want to highlight is the lack of specificity of the test…
NOT a diagnostic test…
feasible screening tool that can reduce the number of tests that physicians order up front…"
Alicia Algeciras-Schimnich PhD
Professor of Laboratory Medicine and Pathology at Mayo Clinic Rochester


"Sensitivity of the new blood test makes it a potentially useful tool for monitoring the effectiveness of new disease-modifying therapies as they become available, and for measuring the outcomes of clinical trials…
Nfl is being positioned to be used as **key biomarker for assessing outcomes in clinical trials**"
Alicia Algeciras-Schimnich PhD
Professor of Laboratory Medicine and Pathology at Mayo Clinic Rochester

Neurofilament Light Chain

The Neurologist's Troponin? ANA?

Key points for Serum Nfl

- Marker of neurodegeneration/neuronal injury NOS
- Elevated NfL is concerning and low NfL is reassuring
- High correlation with CSF Nfl
- High correlation with white matter integrity
- Good sensitivity, very limited clinical specificity
  - If you plan to order, plan to counsel, plan to not have an answer…

Ochsner Health

DON'T PANIC

and ask a Question(s)

References