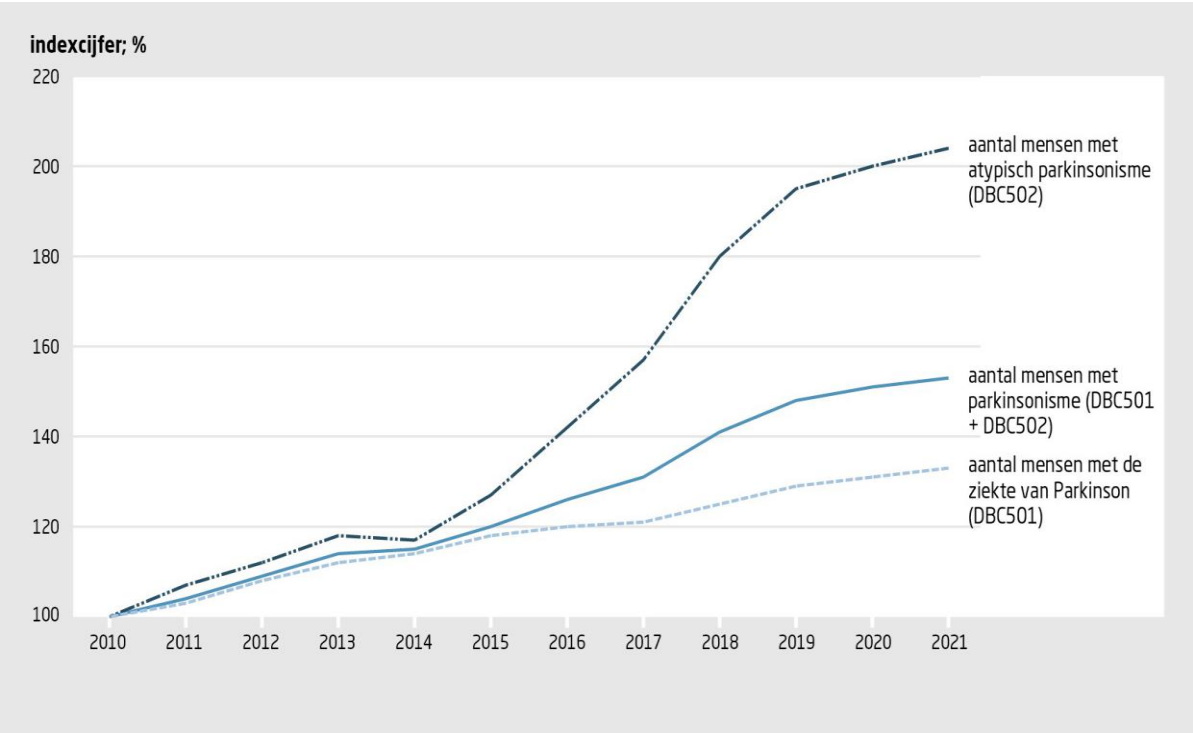
Amsterdam UMC
Universitair Medische Centra

Vroege opsporing van Parkinson met nieuwe biomarkers

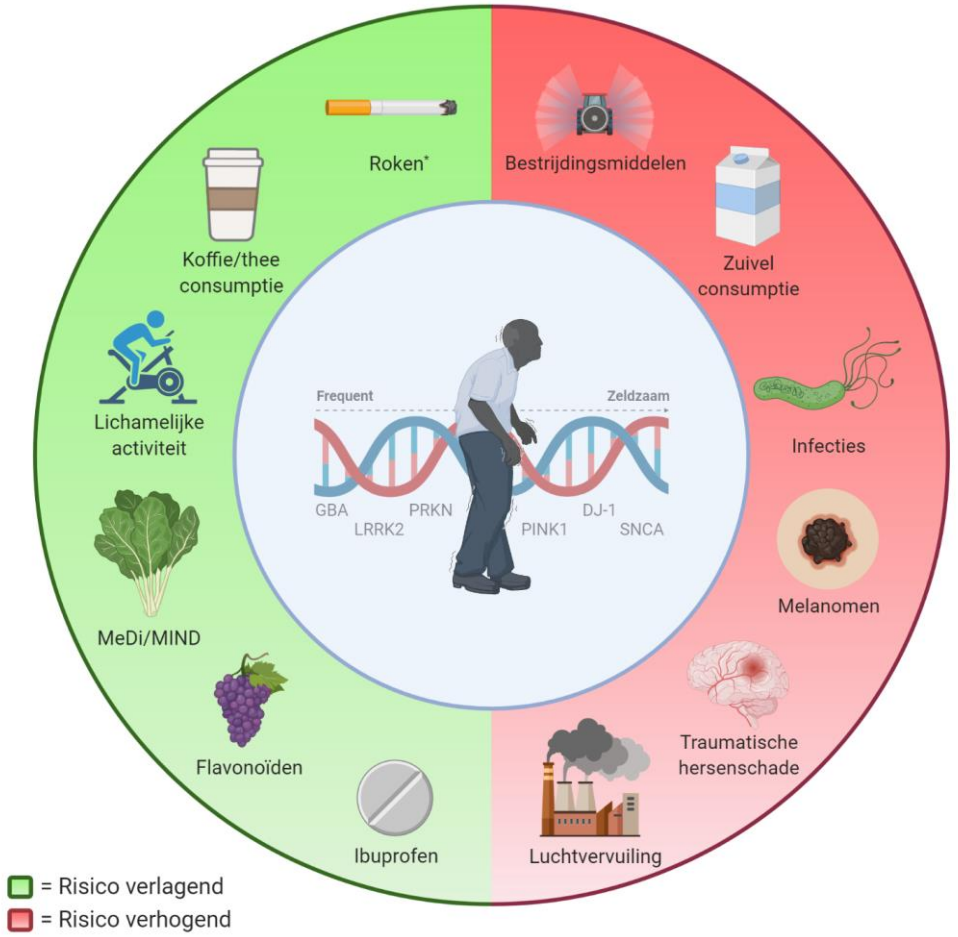
Wilma D.J. van de Berg, PhD, neurowetenschapper, neuroanatoom,
Afdeling Anatomie en Neurowetenschappen, Amsterdam UMC, Vrije Universiteit Amsterdam

Vroege opsporing van Parkinson

Vroege opsporing van Parkinson risicofactoren



In Nederland neemt de prevalentie toe van zowel de ziekte van Parkinson als de overige vormen van parkinsonisme[1].



[1]Van der Gaag et al. NTvG 2023

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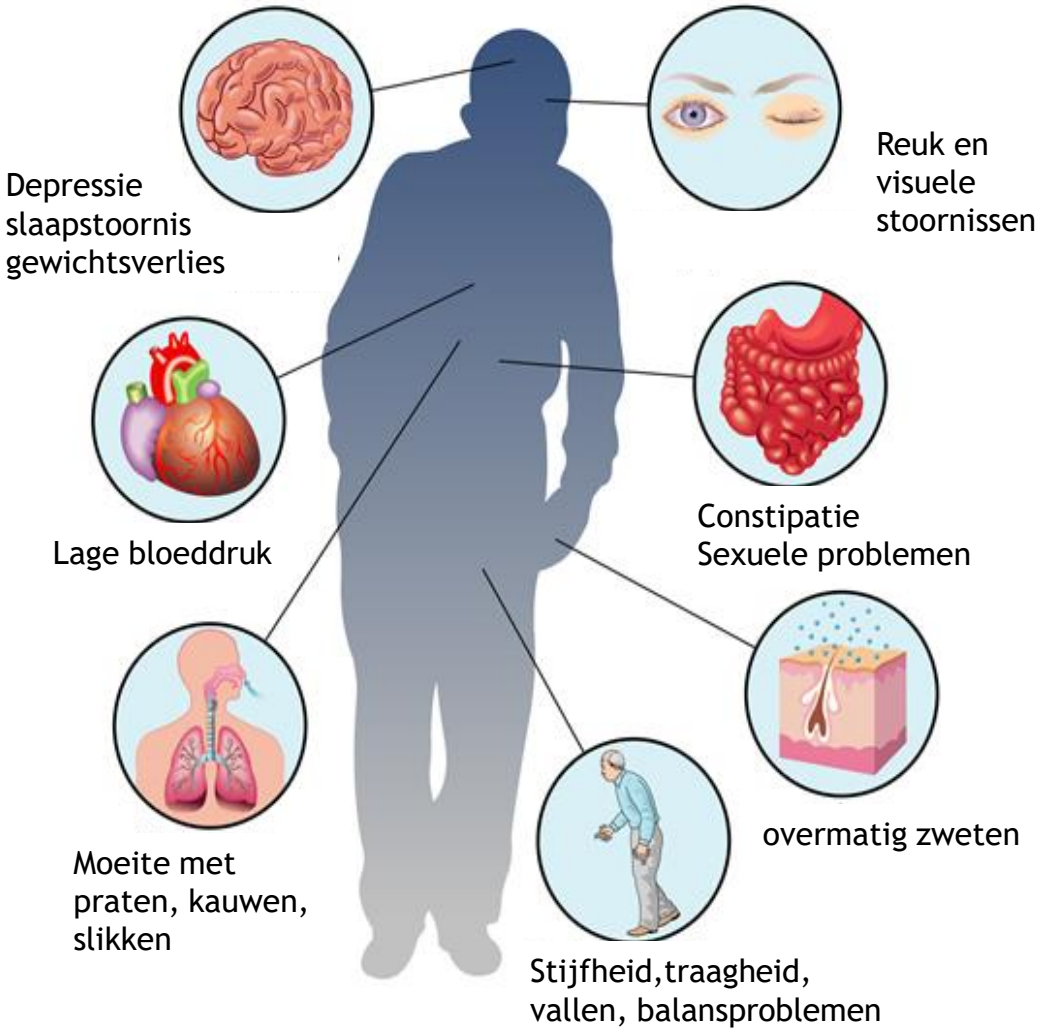
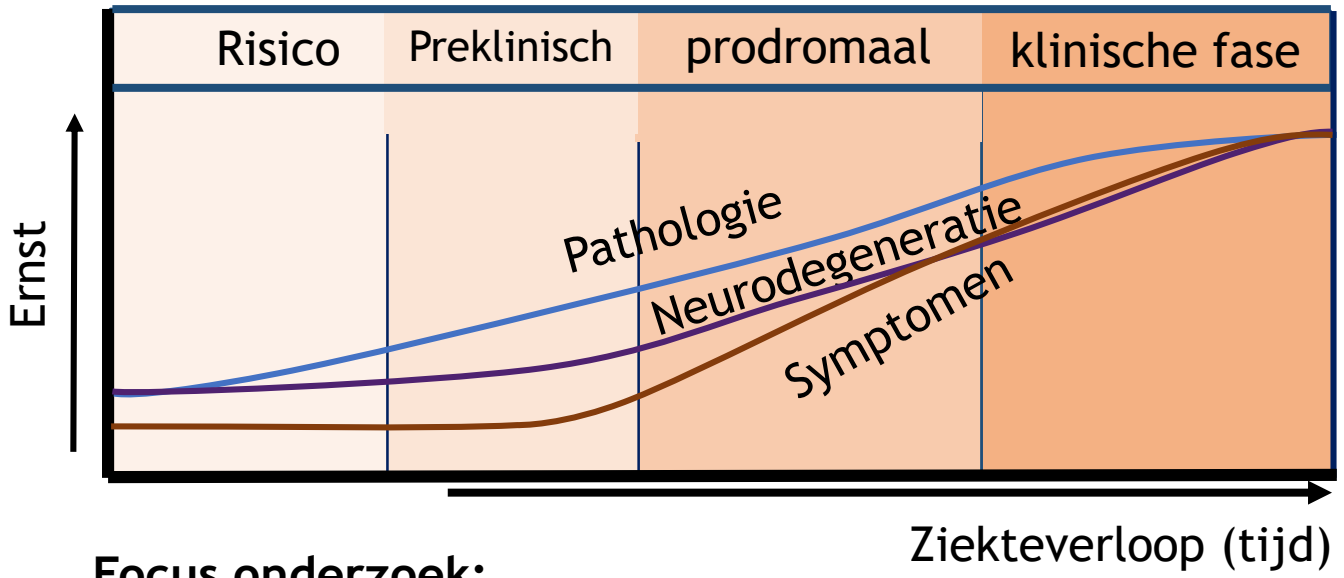
KENMERKEN





Focus onderzoek:

Nieuwe ziekte-remmende behandelingen:

Ontwikkeling van interventies die het ziekteproces kunnen vertragen of stoppen

Vroegdiagnostiek:

Hoe eerder de ziekte ontdekt kan worden, hoe eerder gestart kan worden met medicatie.

Postuma et al. Mov Dis 2015; Postuma and Berg, Nat Rev Neurology 2016

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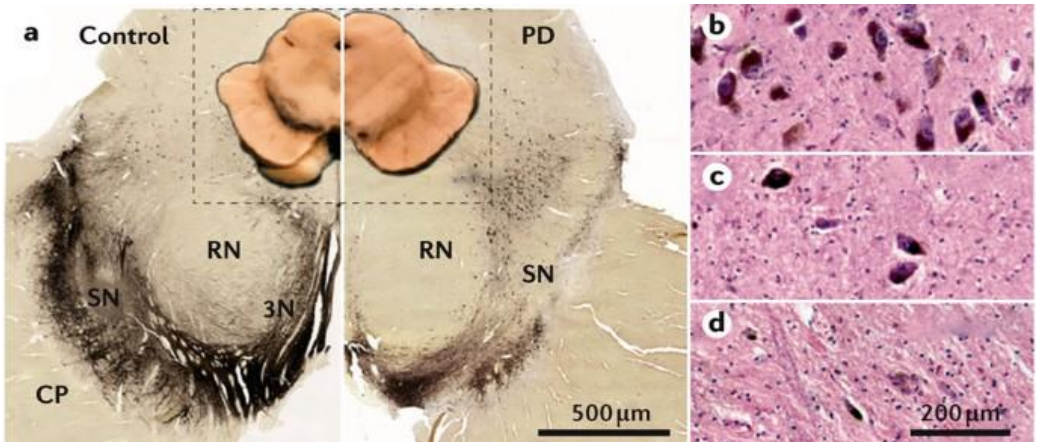
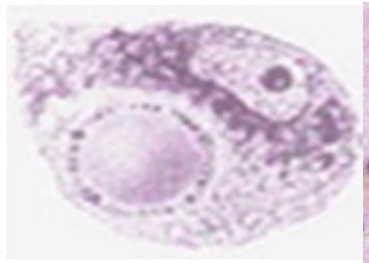
KENMERKEN

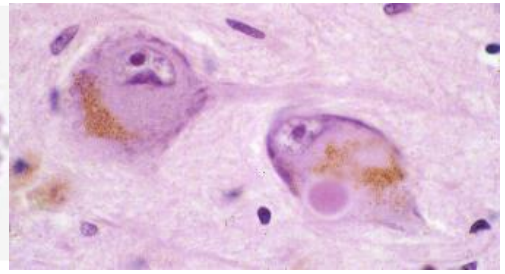
Degeneratie van dopaminerge zenuwcellen

controle Parkinson

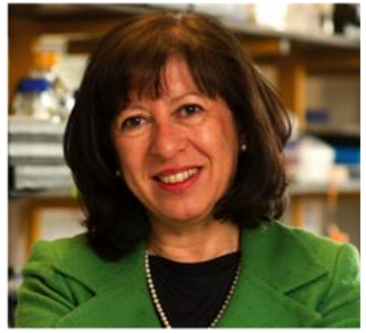


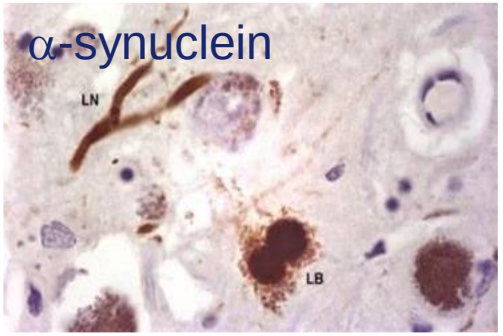
Lewy body pathologie: opstapeling van eiwitten en lipiden





Lewy, 1912





Spillantini, 1997

Stapeling van het eiwit alfa-synucleine in zieke hersencellen is kenmerkend voor de ziekte van Parkinson.

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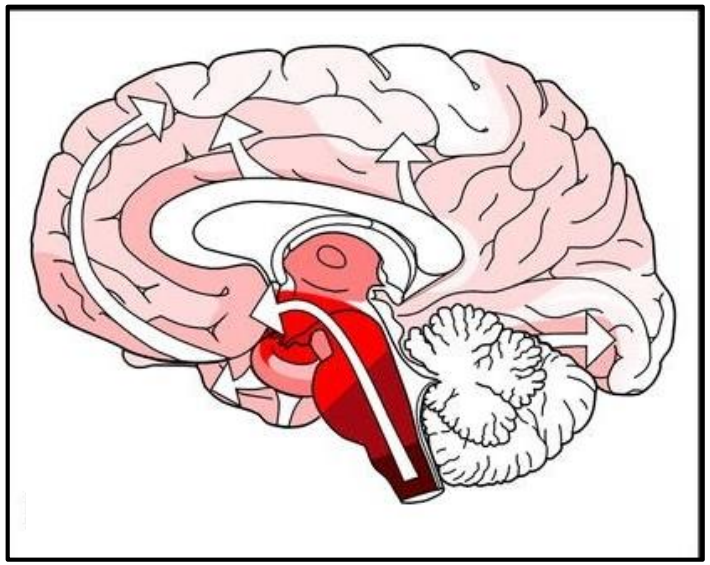
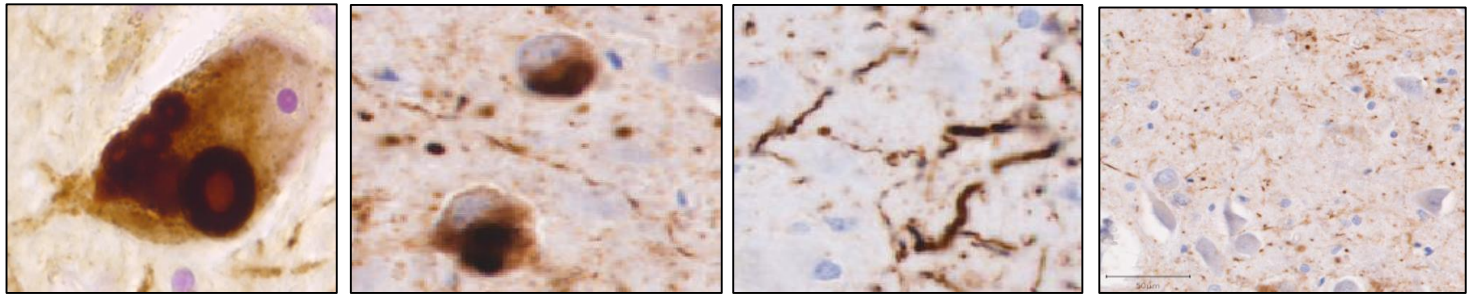
KENMERKEN

- 85% van alle mensen met parkinson hebben Lewy bodies in de hersenen[1].
- Stapeling van het eiwit α-synucleine in Lewy bodies is kenmerkend voor Parkinson en vertoond een vast distributie patroon in de hersenen[2].
- α-Synucleine stapeling is ook te zien in de darmen, het hart, ruggenmerg en huid van mensen met Parkinson.

® Heik Braak, Uni Frankfurt





1. Geut et al. Acta Neuropath Comm 2020; Braak et al. Cell tissue Res 2004; Shahmoradian H et al. *Nature Neuroscience 2019*

Wat zijn de bouwstenen van α-synuclein aggregaten?

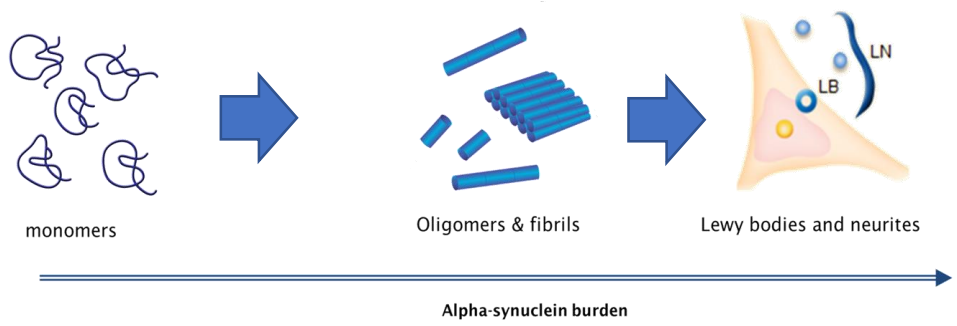
Acta Neuropathologica (2021) 142:423–448
https://doi.org/10.1007/s00401-021-02329-9

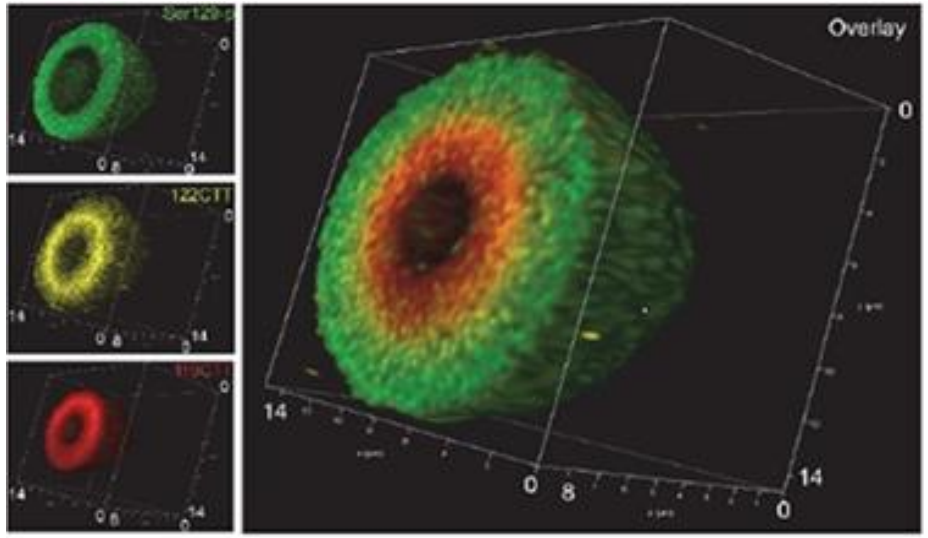
ORIGINAL PAPER

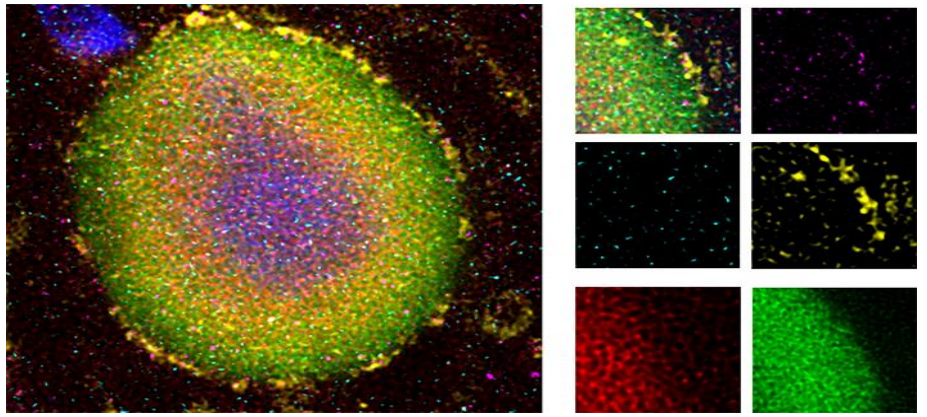
The subcellular arrangement of alpha-synuclein proteoforms in the Parkinson's disease brain as revealed by multicolor STED microscopy

Tim E. Moors[1,10] · Christina A. Maat[1] · Daniel Niedieker[2] · Daniel Mona[3] · Dennis Petersen[2] · Evelien Timmermans-Huisman[1] · Jeroen Kole[4] · Samir F. El-Mashtoly[2] · Liz Spycher[3] · Wagner Zago[5] · Robin Barbour[5] · Olaf Mundigl[6] · Klaus Kaluza[6] · Sylwia Huber[7] · Melanie N. Hug[7] · Thomas Kremer[3] · Mirko Ritter[8] · Sebastian Dziadek[9] · Jeroen J. G. Geurts[1] · Klaus Gerwert[2] · Markus Britschgi[3] · Wilma D. J. van de Berg[1]

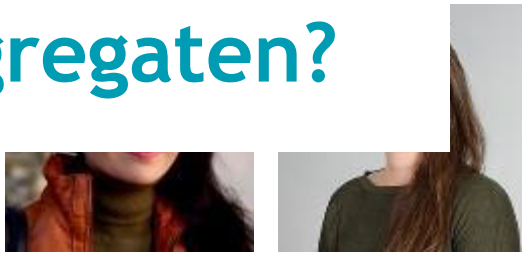
Received: 21 February 2021 / Revised: 11 May 2021 / Accepted: 12 May 2021 / Published online: 11 June 2021







Wat zijn de bouwstenen van α-synuclein aggregaten?



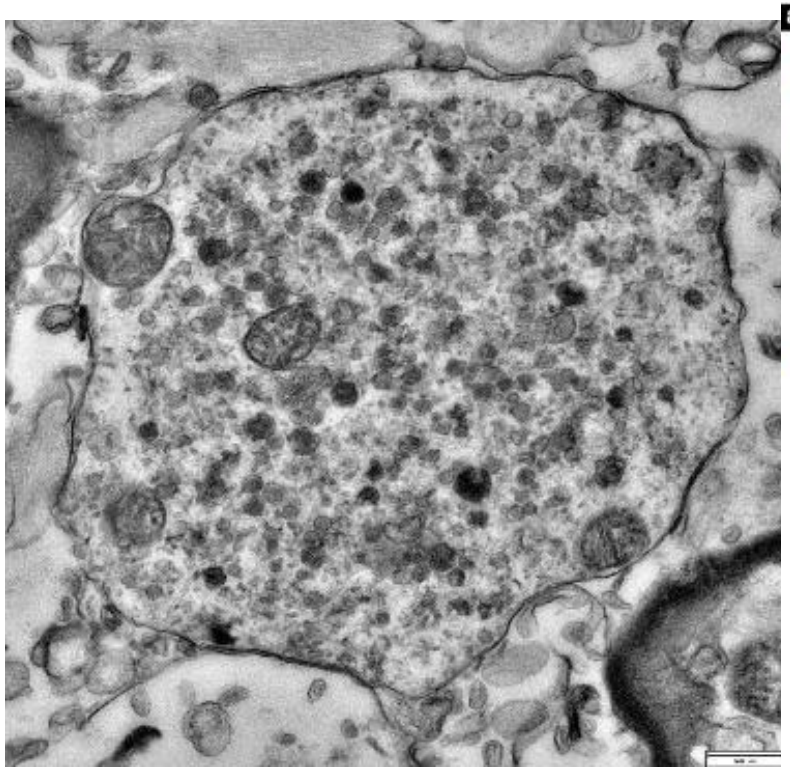
Article | Published: 24 June 2019

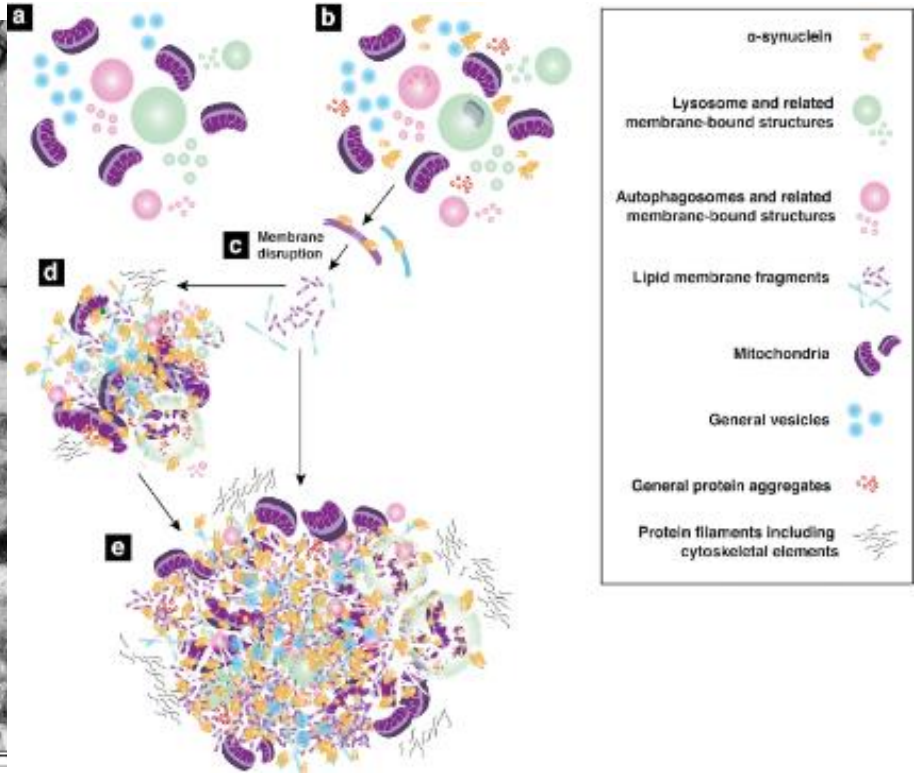
Lewy pathology in Parkinson's disease consists of crowded organelles and lipid membranes

Sarah H. Shahmoradian, Amanda J. Lewis, Christel Genoud, Jürgen Hench, Tim E. Moors, Paula P. Navarro, Daniel Castaño-Díez, Gabriel Schweighauser, Alexandra Graff-Meyer, Kenneth N. Goldie, Rosmarie Sütterlin, Evelien Huisman, Angela Ingrassia, Yvonne de Gier, Annemieke J. M. Rozemuller, Jing Wang, Anne De Paepe, Johannes Erny, Andreas Staempfli, Joerg Hoernschemeyer, Frederik Großerüschkamp, Daniel Niedieker, Samir F. El-Mashtoly, Marialuisa Quadri, Wilfred F. J. Van IJcken, Vincenzo Bonifati, Klaus Gerwert, Bernd Bohrmann, Stephan Frank, Markus Britschgi, Henning Stahlberg ✉, Wilma D. J. Van de Berg ✉ & Matthias E. Lauer ✉ -Show fewer authors

Nature Neuroscience **22**, 1099–1109(2019) | Cite this article

12k Accesses | **61** Citations | **174** Altmetric | Metrics



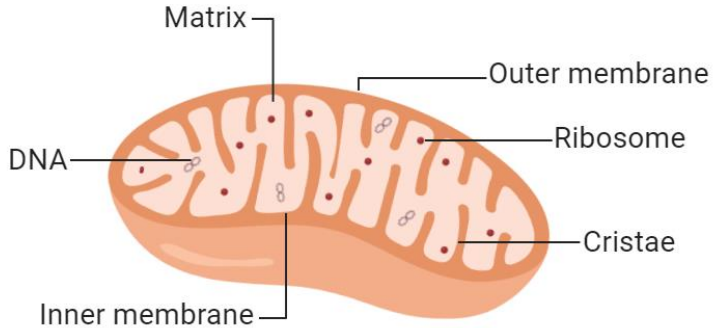


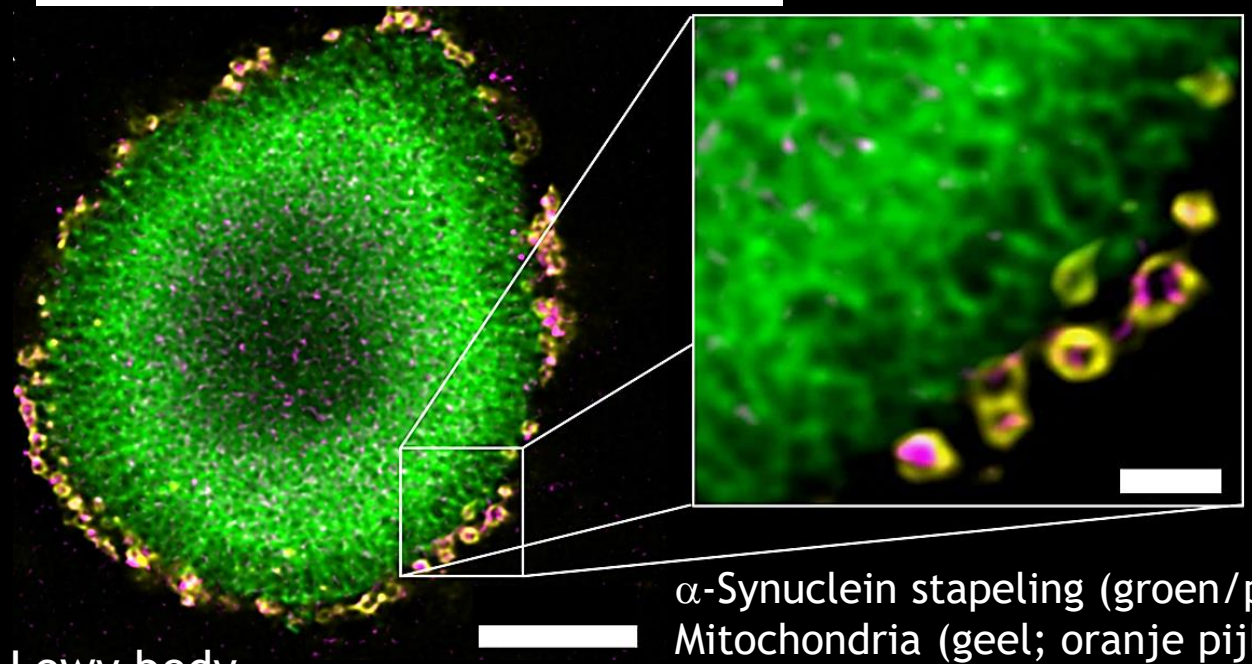
- α-Synuclein aggregaten in zenuwcellen bevatten >300 eiwitten, organellen, membrane en lipiden.
- Theory: *a-synuclein may mediate fusion of disrupted membranes which leads to the formation of Lewy bodies and neurites – key pathological hallmarks of Parkinson's disease*

Shahmoradian H et al. *Nature Neuroscience 2019*

Stapeling van mitochondria in Lewy bodies

Mitochondria= energie centrale

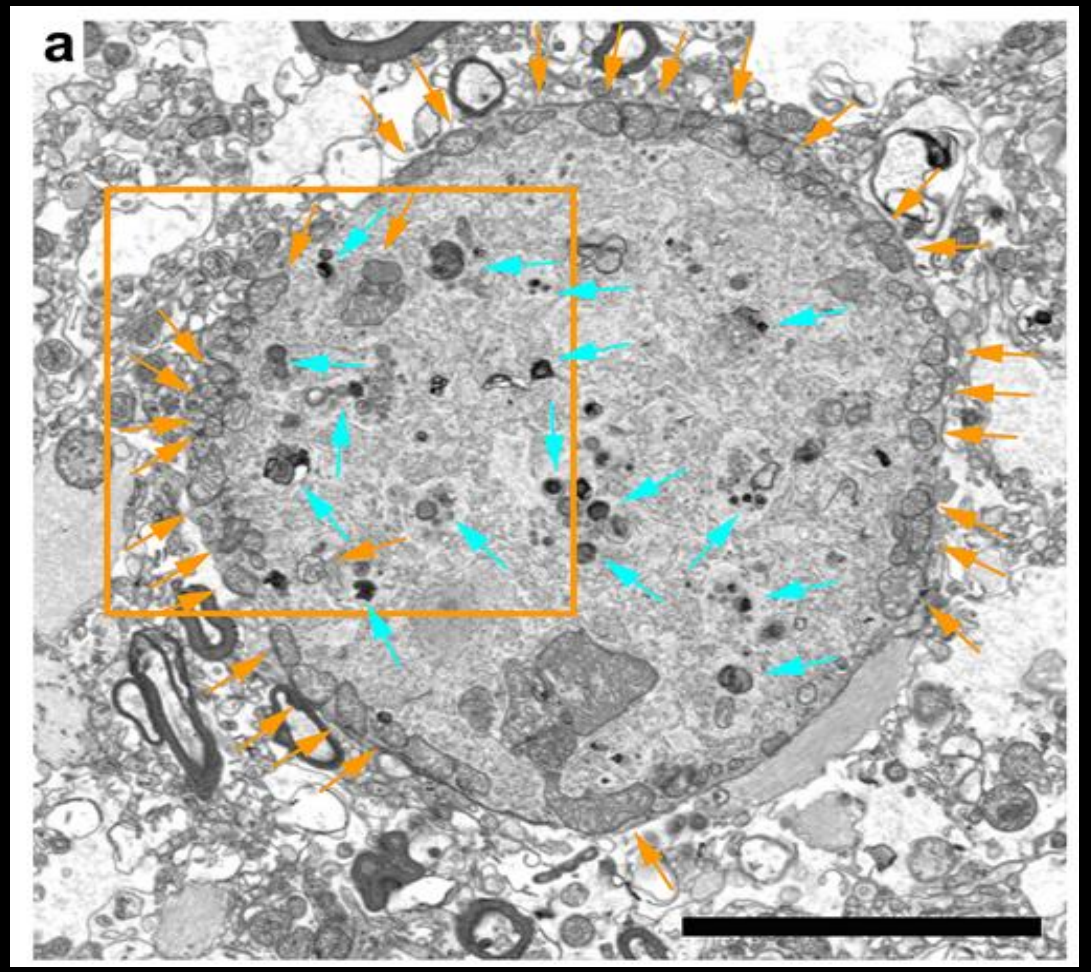




Lewy body

α-Synuclein stapeling (groen/paars)
Mitochondria (geel; oranje pijl)
Lysosomen (aqua pijl)

Lewy body



Shahmoradian H et al. *Nature Neuroscience 2019*

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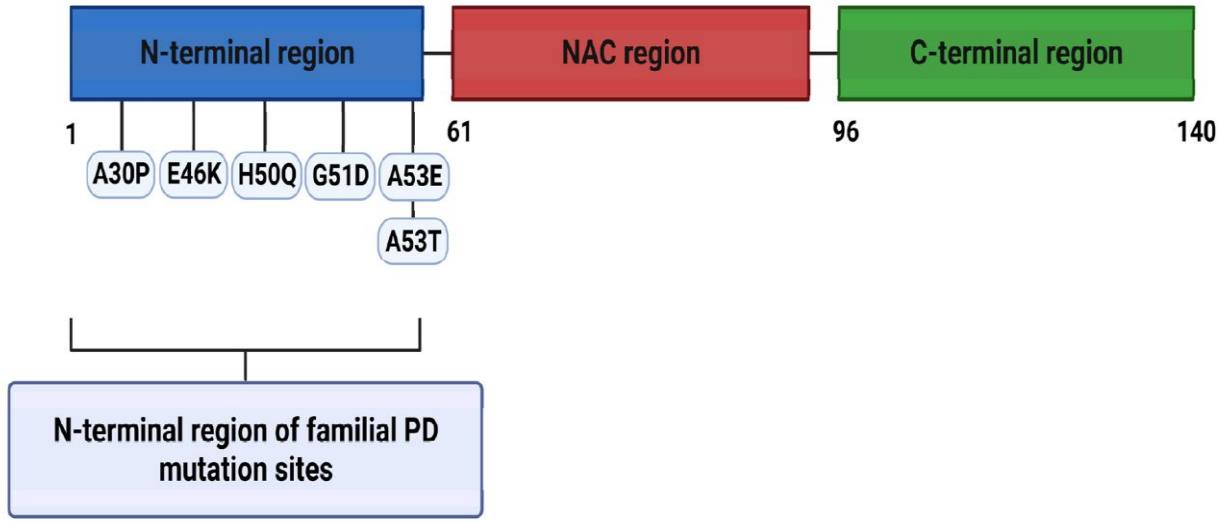
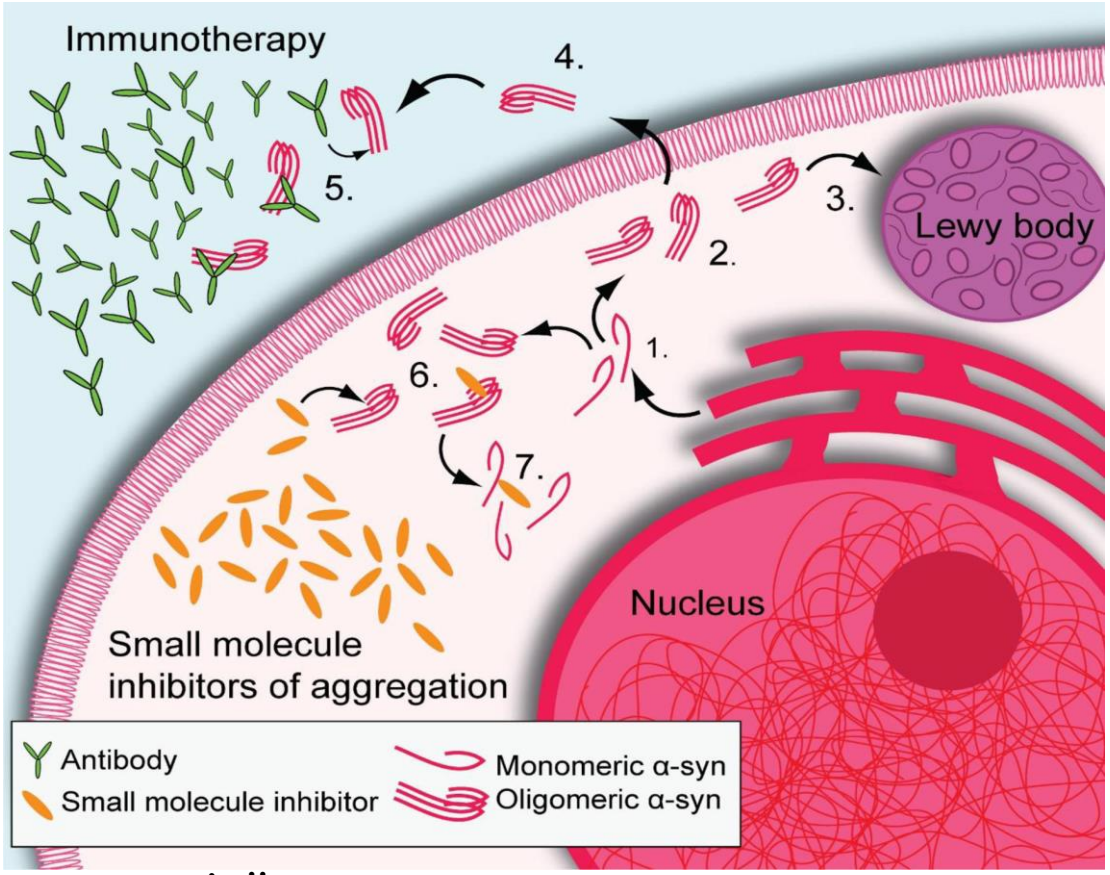
ZIEKTE MECHANISMEN: α-SYNUCLEIN

α-Synucleine eiwit



Immunologische interventies strategieën om α-Synuclein aggregatie te remmen



Andere strategieën:

- Gen-therapy: aSyn expressie beinvloeden
- small molecules die aSyn remmen of afbraak bevorderen

1. Rodger et al. Int J Mol Sci 2023; Stott et al. Prog Brain Res 2020

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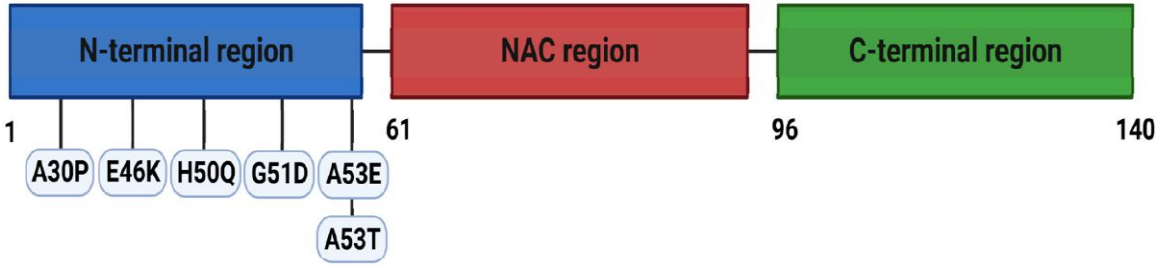
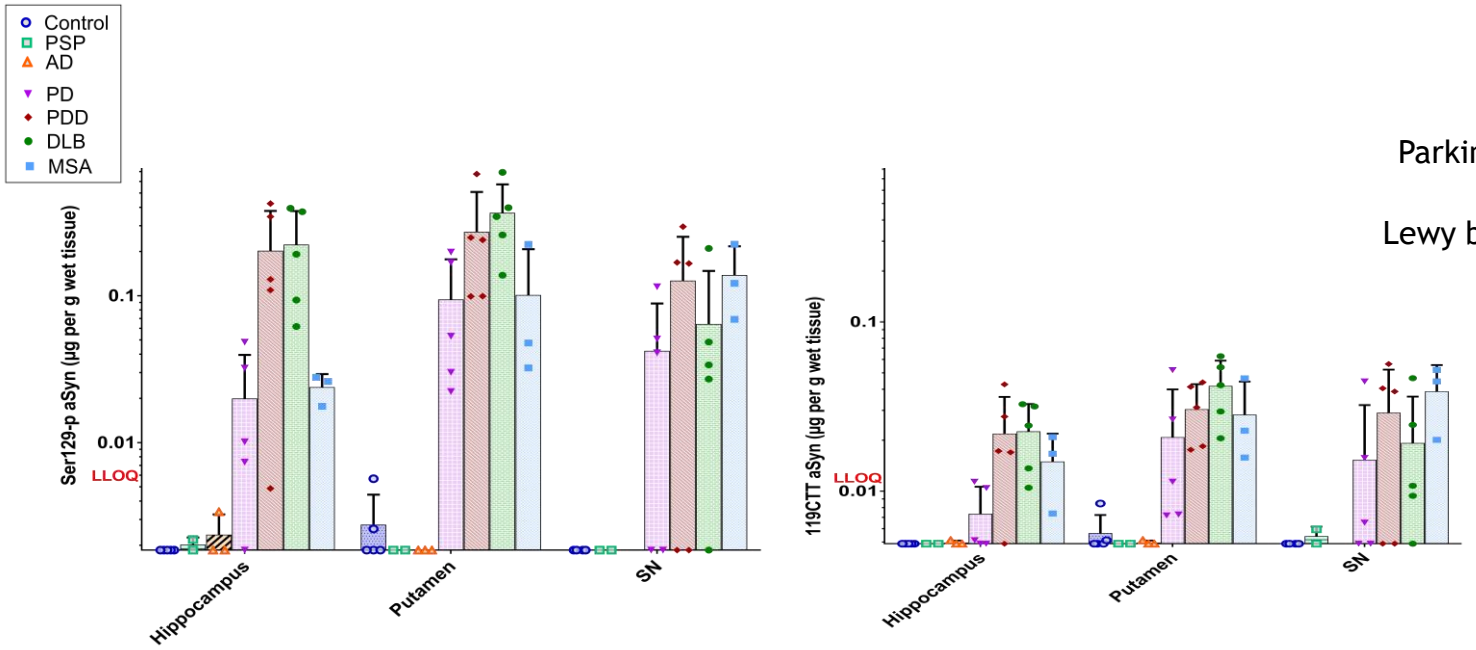
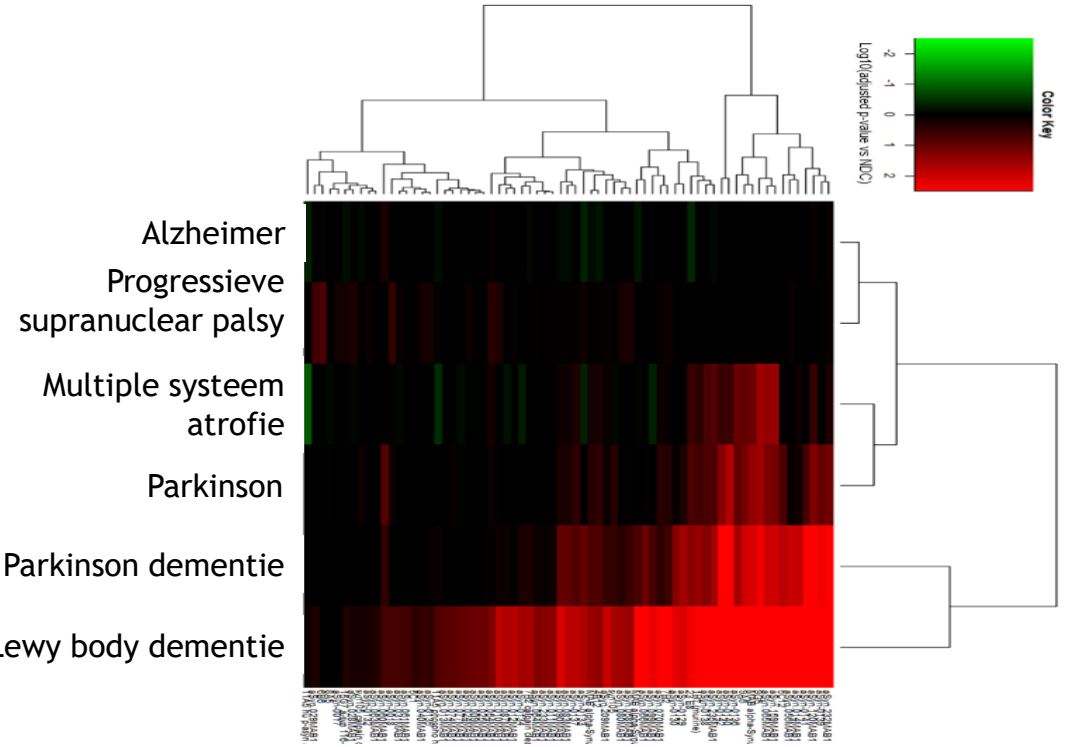
STAPELING VAN ALFA-SYNUCLEINE







α-Synucleine stapeling in de hersenen in kenmerkend voor de ziekte van Parkinson, multiple systeem atrofie en Lewy body dementie

Moors et al. Acta Neuropathol Comm. 2022

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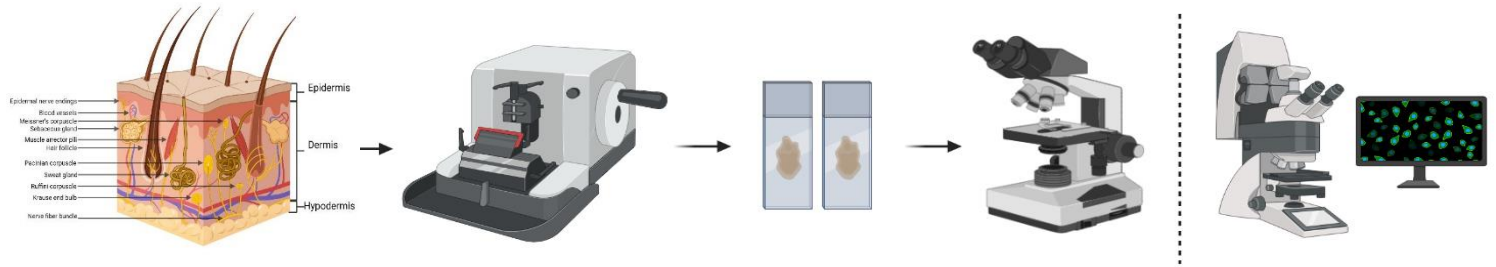
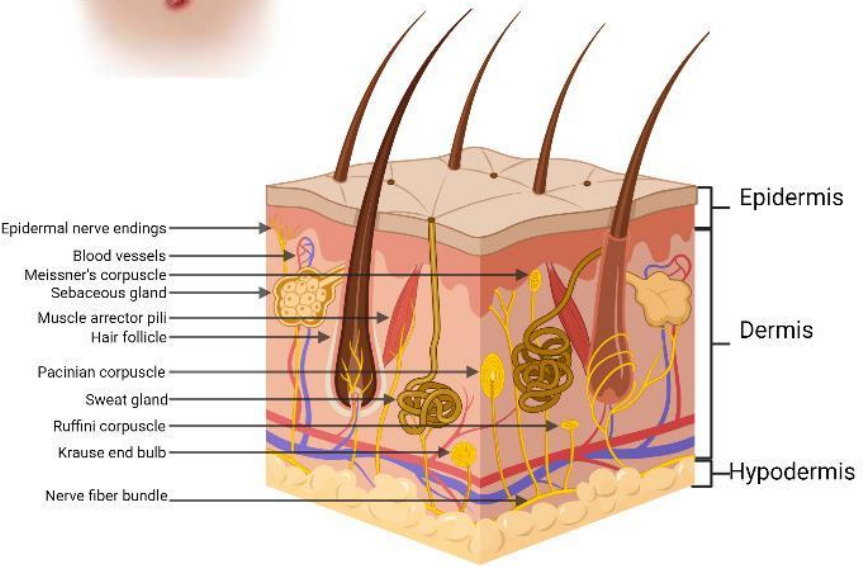
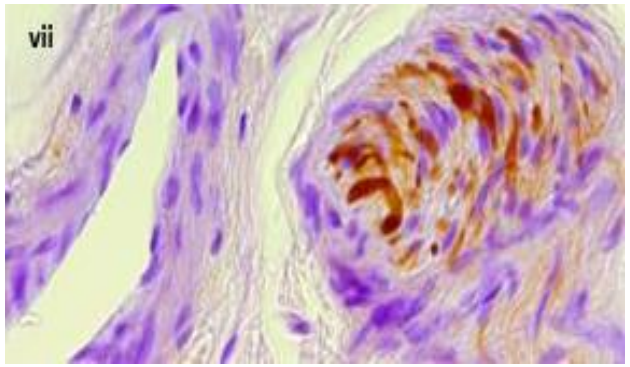
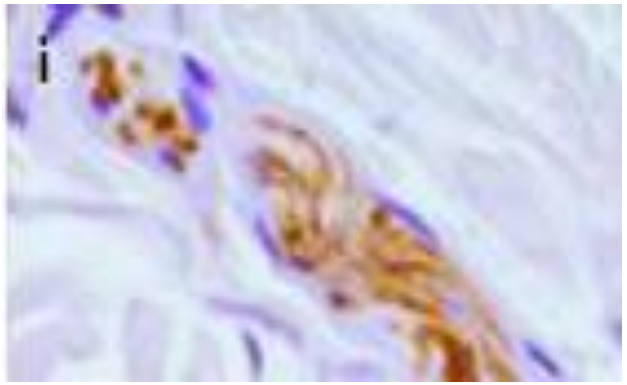
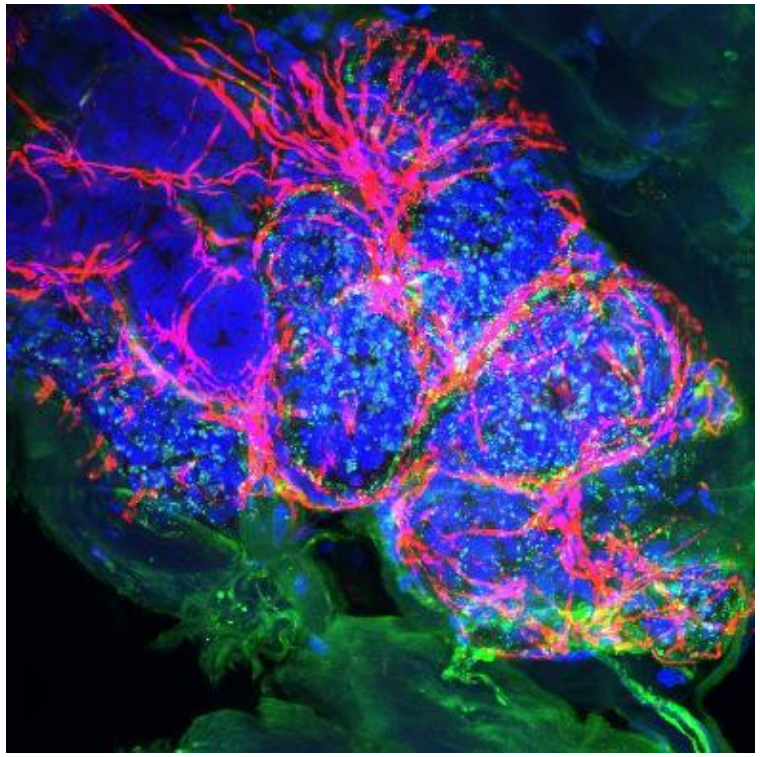
BIOMARKERS: α-SYNUCLEINE STAPELING IN HUIDWEEFSEL











Van der Gaag, in prep

α-synucleine stapeling (bruin of groen) in de huid van een Parkinson patient

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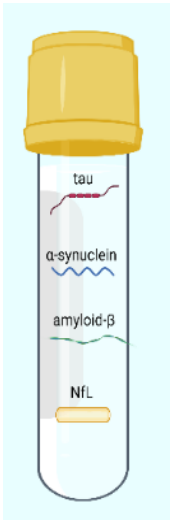
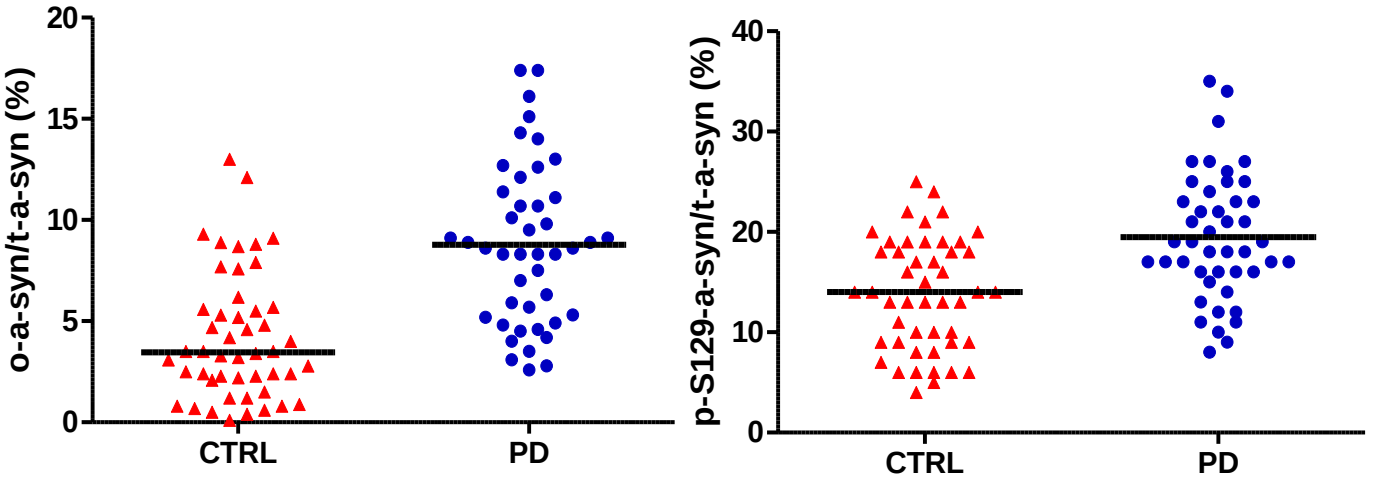
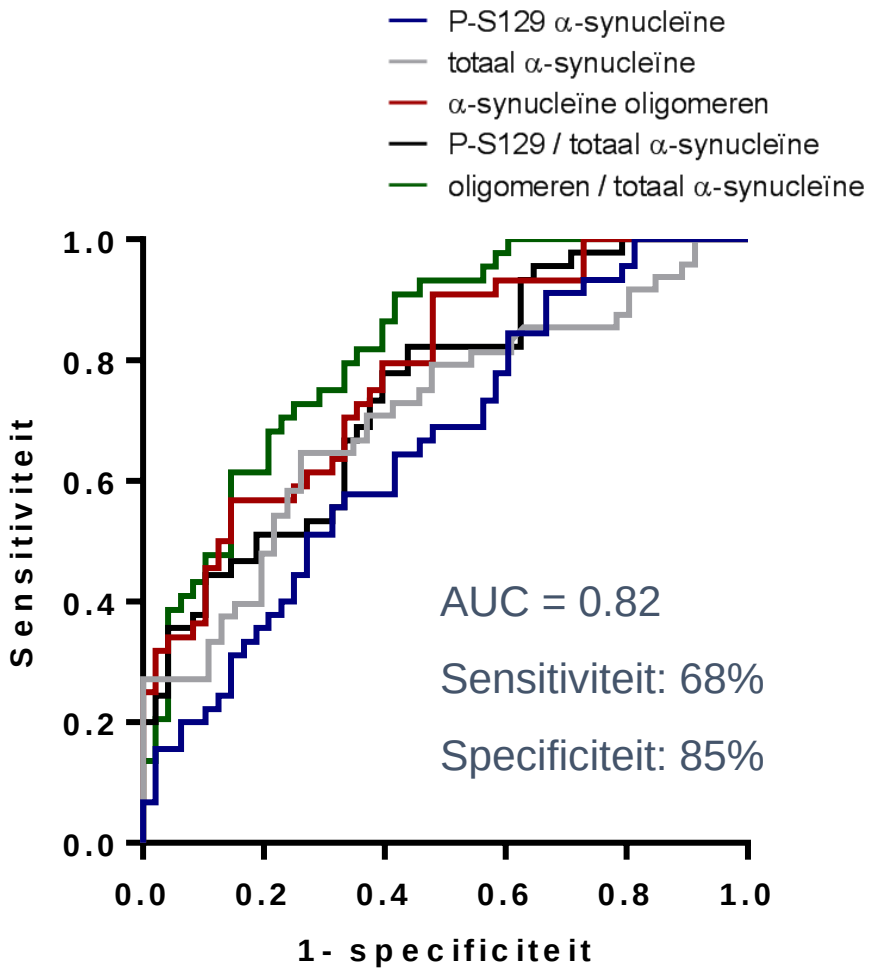
BIOMARKERS: α-SYNUCLEIN STAPELING IN HERSENVOCHT





α-Synuclein expressie in hersenvocht van controles (red) en mensen met Parkinson (blauw)



Majbour et al. Mol Neurodeg 2016

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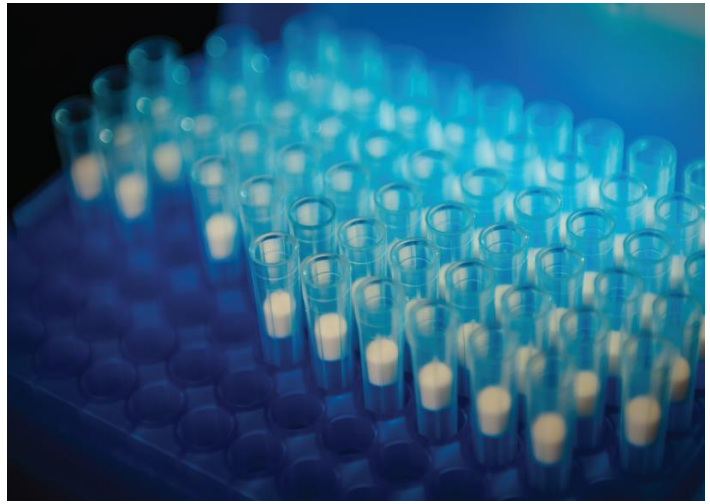
BIOMARKERS: α-SYNUCLEIN STAPELING IN HERSENVOCHT

Breaking News: Parkinson's Disease Biomarker Found
April 13, 2023



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Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study

Andrew Siderowf, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kieburtz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†*

Lancet Neurol 2023; 22: 407–17

	N	Specificity (95% CI)	Sensitivity (95% CI)
Healthy controls	163	96·3% (93·4–99·2)	NA
SWEDD	54	90·7% (83·0–98·5)	NA
All Parkinson's disease cases	545	NA	87·7% (84·9–90·5)
Hyposmic	390	NA	97·2% (95·5–98·8)
Normosmic	146	NA	63·0% (55·2–70·8)
Sporadic Parkinson's disease	373	NA	93·3% (90·8–95·8)
LRRK2 mutation Parkinson's disease	123	NA	67·5% (59·2–75·8)
GBA mutation Parkinson's disease	49	NA	95·9% (90·4–100·0)
LRRK2 mutation Parkinson's disease			
Male participants	65	NA	78·5% (68·5–88·5)
Female participants	58	NA	55·2% (42·4–68·0)
Hyposmic	69	NA	89·9% (82·7–97·0)
Normosmic	49	NA	34·7% (21·4–48·0)
Normosmic and female participants	24	NA	12·5% (4·3–31·0)

NA=not applicable. SWEDD=participants with scans without evidence of dopaminergic deficit.

Table 2: **Sensitivity of CSF α-synuclein seed amplification assay for Parkinson's disease, and specificity for healthy controls and SWEDD**

Belangrijkste bevindingen:

- Sensitiviteit voor detectie van α-Synucleine stapeling in Parkinson is 87.7%, specifiteit 96.3%.
- Van de mensen in prodromale fase (hyposmie of slaapstoornis) of at-risk hadden 86% reeds een positieve test-uitslag.

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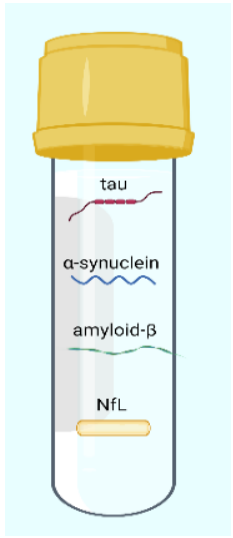
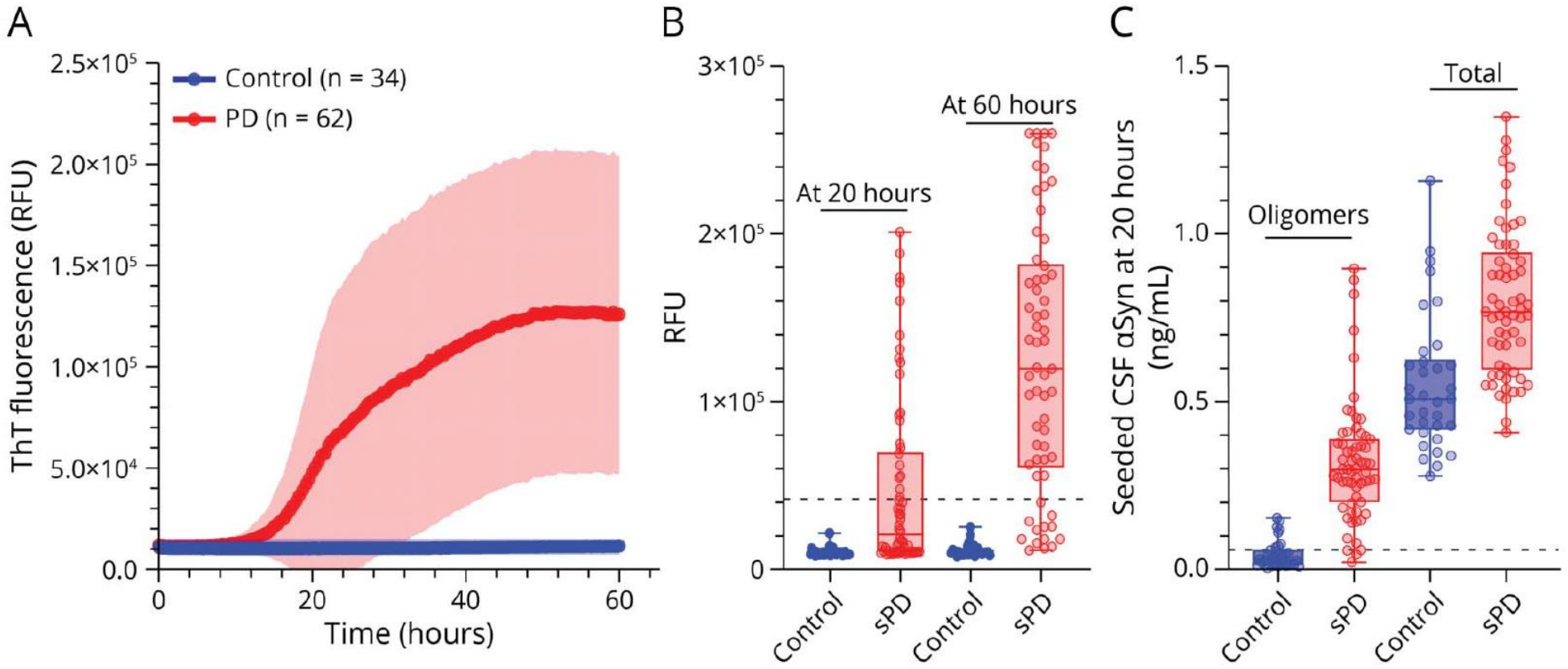
BIOMARKERS: α-SYNUCLEIN STAPELING IN HERSENVOCHT





α-Synuclein stapeling (RT-Quic reactie) in hersenvocht van controles (blauw) en mensen met Parkinson (red)

Majbour et al. Neurology 2022

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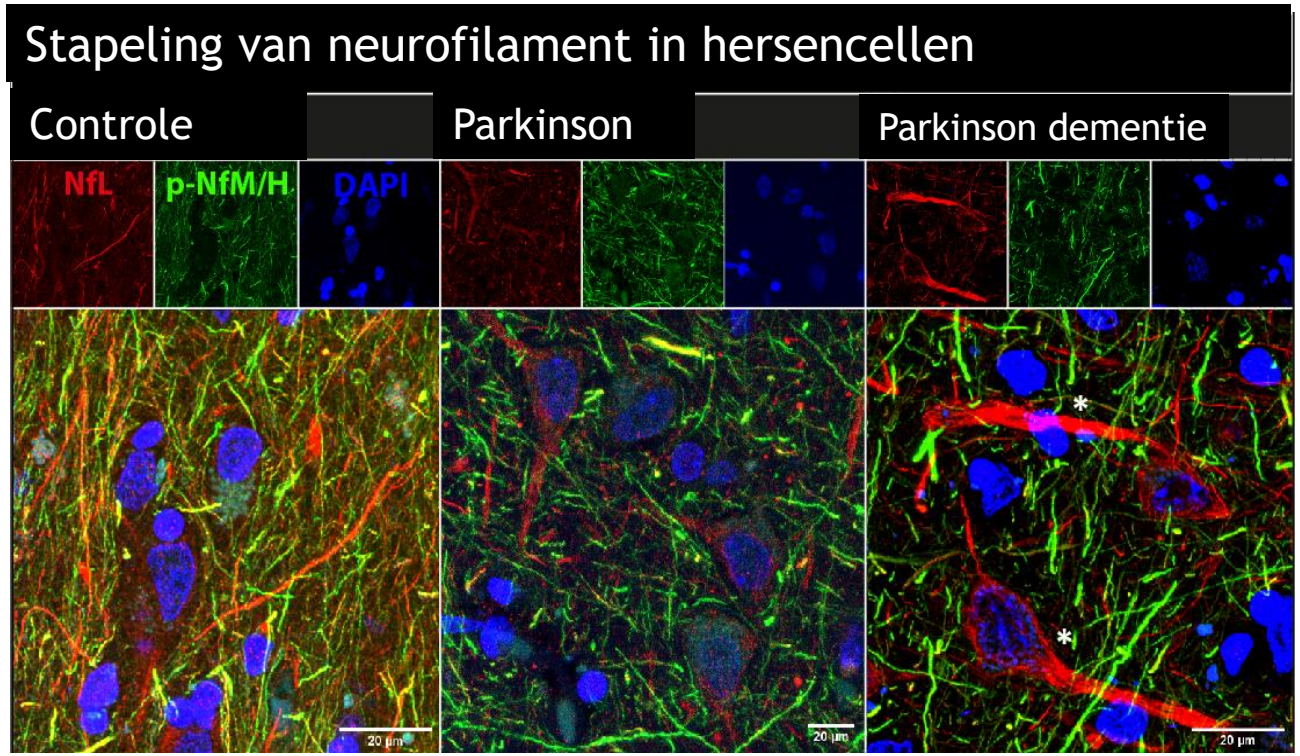
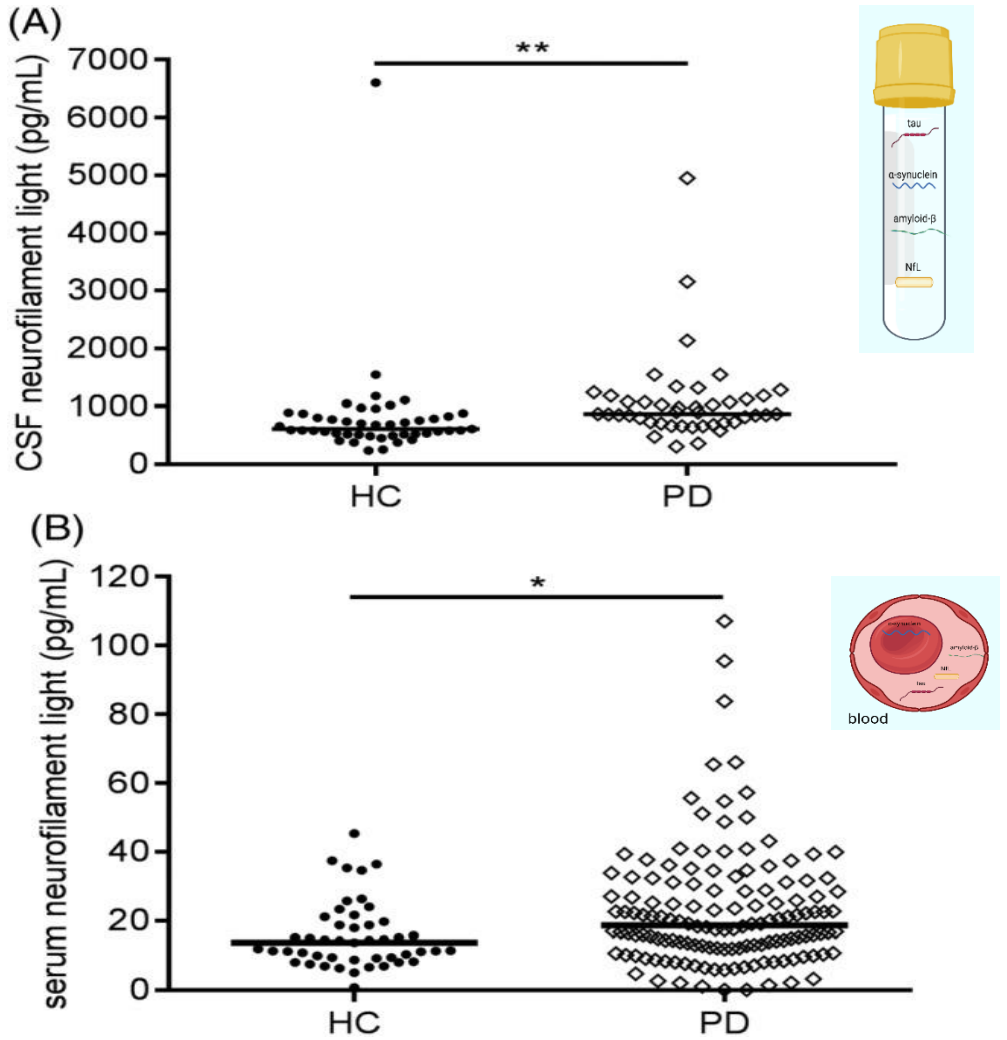
BIOMARKERS: NEUROFILAMENT STAPELING IN HERSENVOCHT EN BLOED



Neurofilament (= red); een mate voor axonale schade



Frigerio et al. Translational Neurodegeneration 2023; Oosterveld et al. 2020

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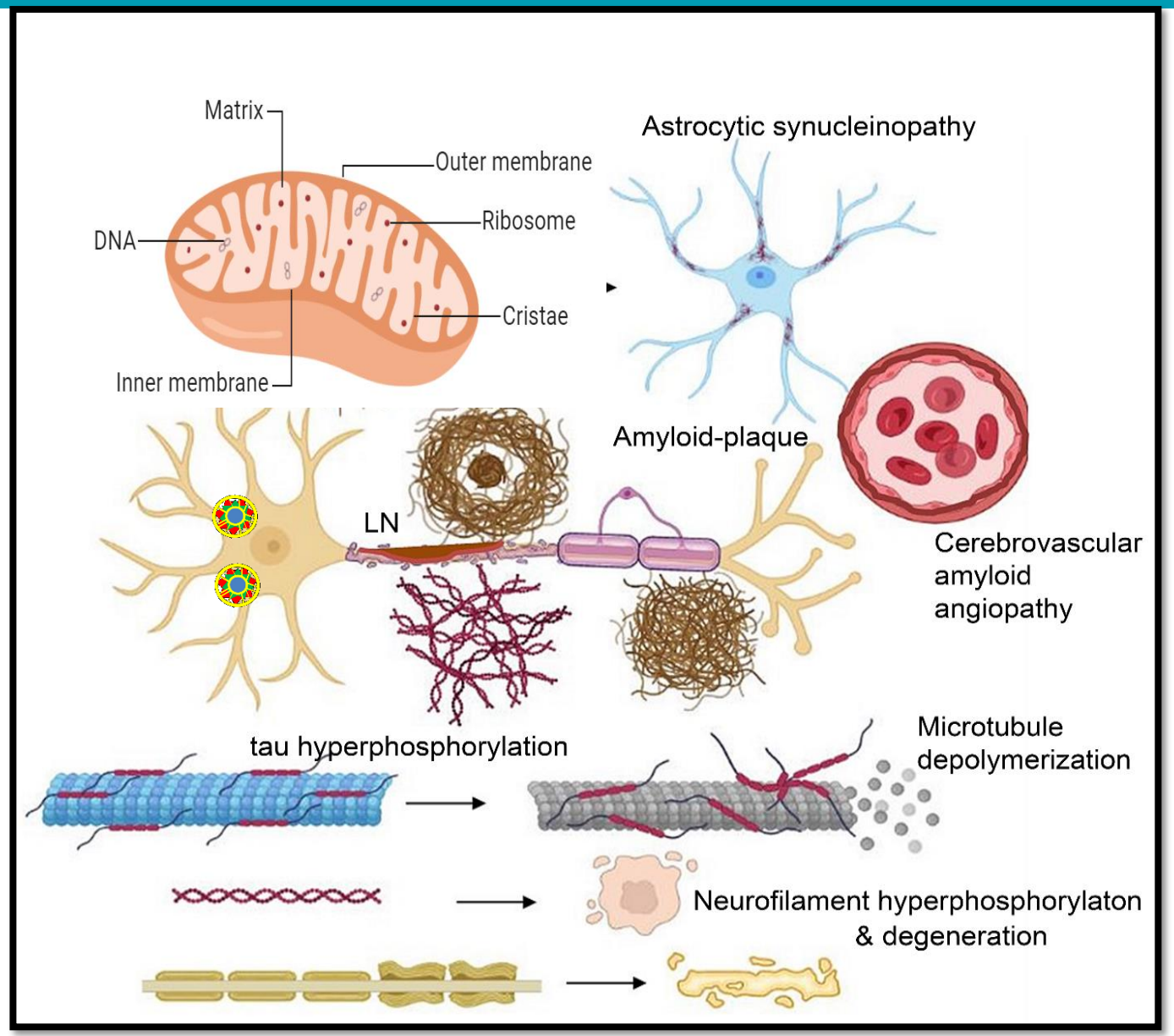
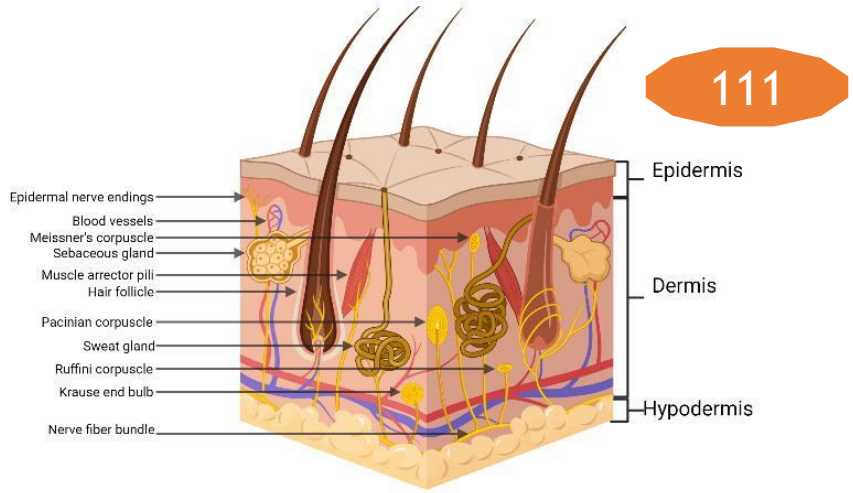
PATHOLOGIE IN HUID HERSENVOCHT EN BLOED





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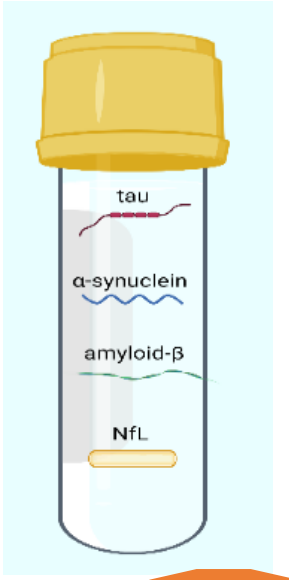

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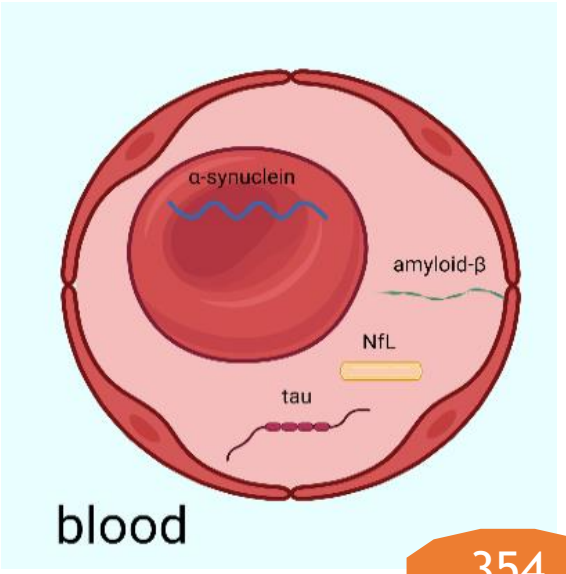

354

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ProPARK: studie design

ProPark

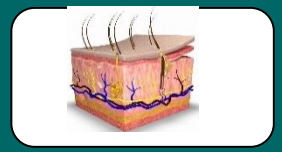
ANALYSIS

KLINISCHE DATABANK

1000 PATIENTEN
250 CONTROLES

- KLINISCHE INFORMATIE
- OBJECTIEVE THUISMETINGEN
- MEDICATIE + BIJWERINGEN

BIOBANK

DATA ANALYSE

ZIEKTE VAN PARKINSON
ParKCode: biomateriaal

Longitudinale (jaarlijkse) verzameling

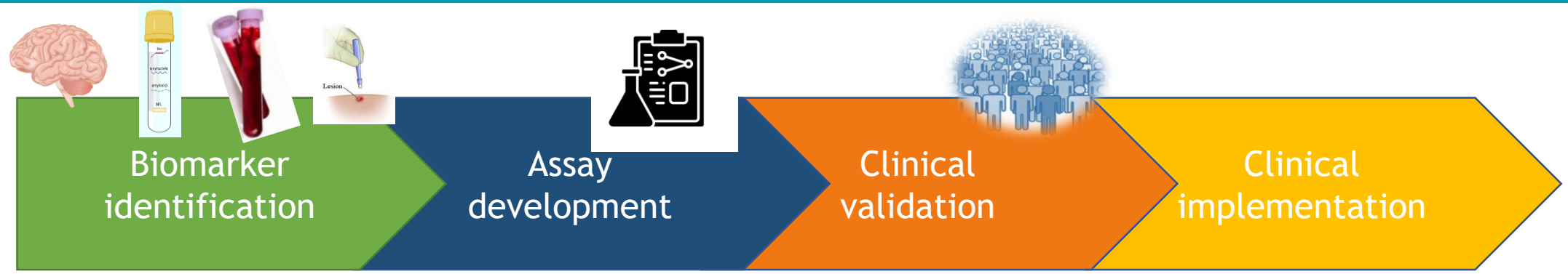
- hersen vocht
- plasma
- serum
- Bloed cellen
- DNA
- RNA
- huid biopt
- ontlasting

Nederlandse hersenbank

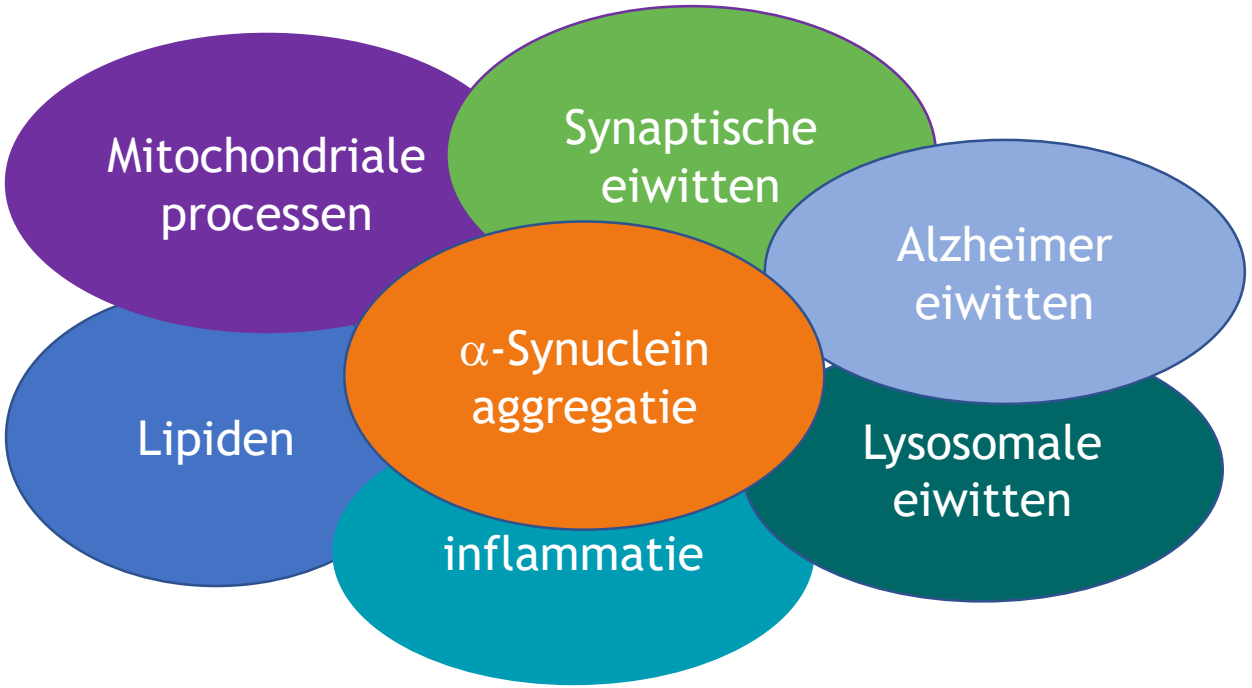
- hersenen
- huidbiopt

ZIEKTE VAN PARKINSON

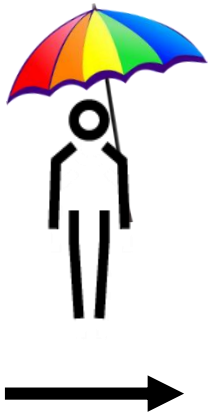
BIOMARKERS: VROEGE OPSPORING VAN ZIEKTEMECHANISME



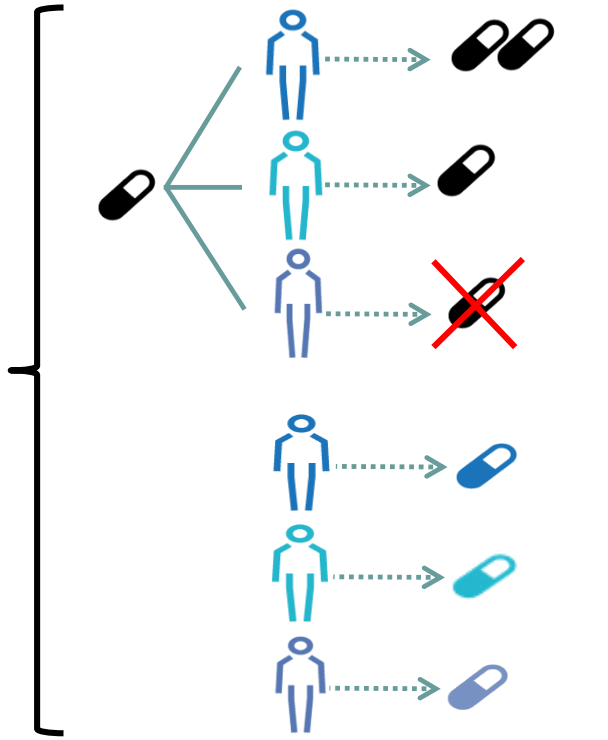
ParKCODE: Een biologische Parkinson code



TOEKOMST PARKINSON
VROEGDIAGNOSTIEK EN MAATWERK



Reduceren bijwerkingen



Behandeling ziekteproces

Van de Berg in prep

Samenwerken

ProParK

aan de behandeling van morgen

www.proparkinson.nl

propark@lumc.nl