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FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

DISEASE MODIFICATION TUSSEN HOOP EN VREES

Arnout Bruggeman

28/09/2022

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UZ GENT

VIB science meets life

fwo

BIOCODEX MICROBIOTA FOUNDATION

VPL VLAAMSE PARKINSON LIGA

MOVING MOUNTAINS FOR PARKINSON'S

parkili.be

DISEASE MODIFYING THERAPIES

- Wat is een disease modifying behandeling?
  1. Ziekteproces stoppen (of vertragen)

  2. Neuroprotectie
     (nog aanwezige neuronen beschermen)

  3. Reeds geleden schade herstellen
     (‘de klok terugdraaien’)

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DISEASE MODIFYING THERAPIES

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ZIEKTEPROCES BEÏNVLOEDEN

- Op welke manier dit onderzoeken?

- Wat is het onderliggende ziekteproces?

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ZIEKTEPROCES BEÏNVLOEDEN

- Op welke manier dit onderzoeken?

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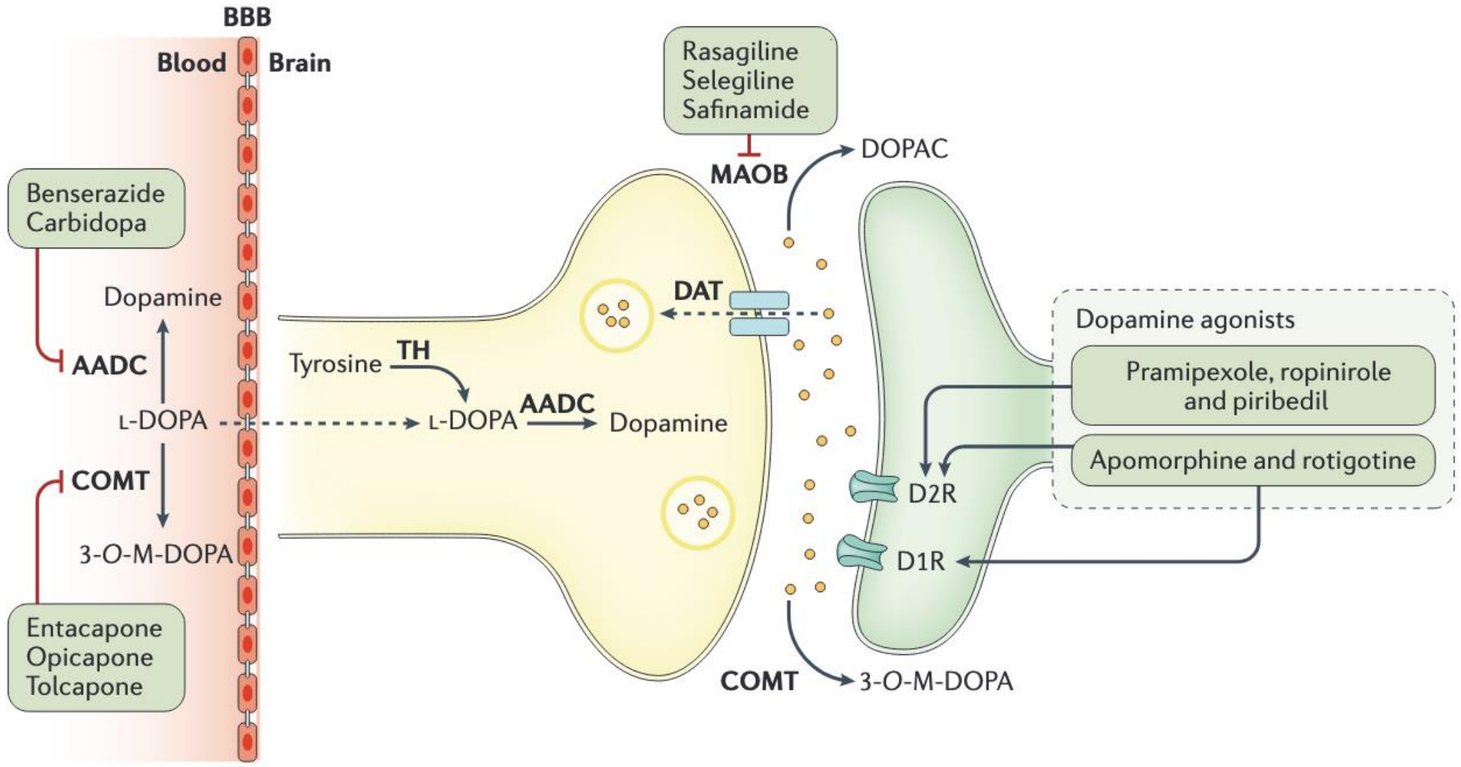
SYMPTOMATISCHE BEHANDELINGEN

– Argumenten voor disease modification bij de symptomatische behandelingen?



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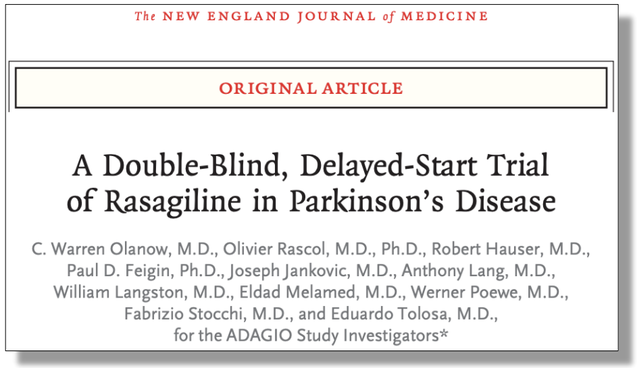
MAO-B INHIBITOREN

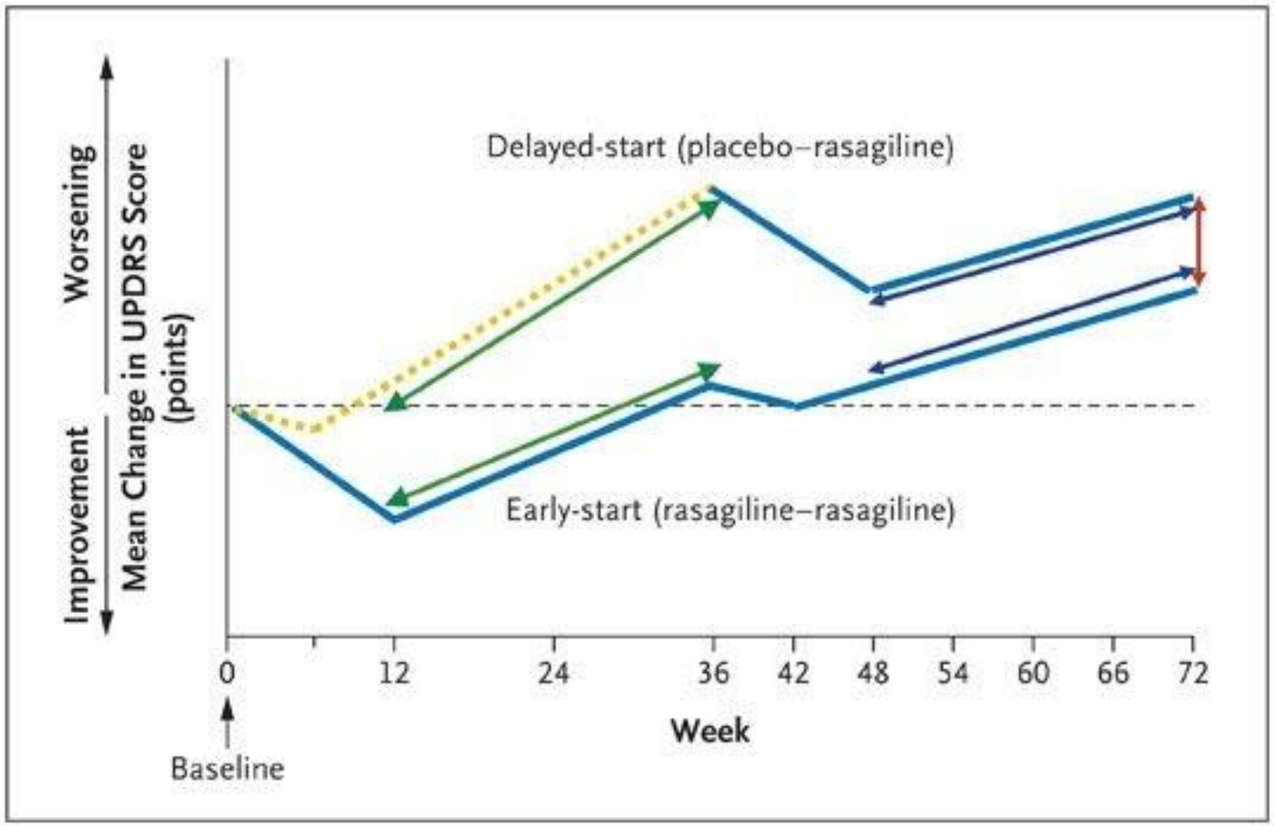
– **Azilect**

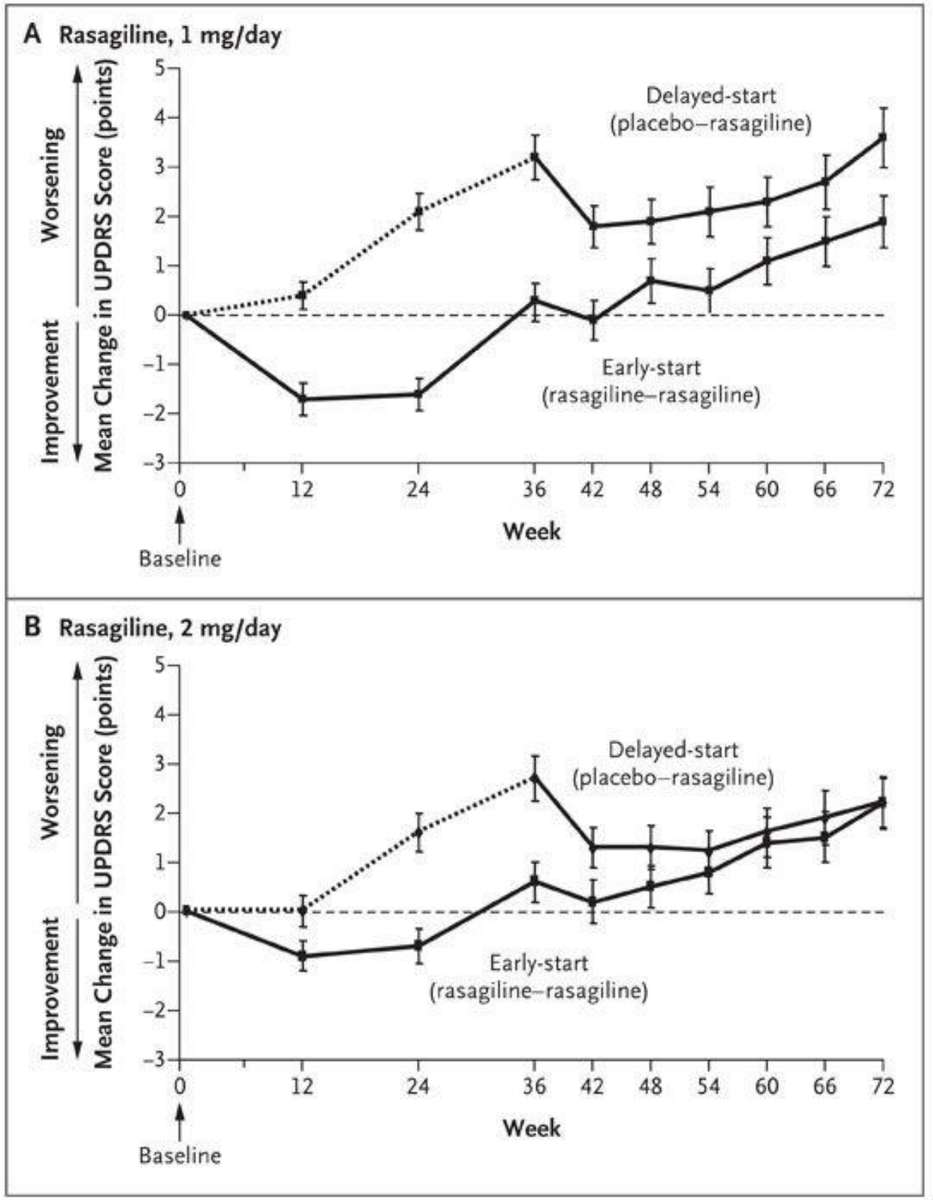

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Double-Blind, Delayed-Start Trial of Rasagiline in Parkinson's Disease

C. Warren Olanow, M.D., Olivier Rascol, M.D., Ph.D., Robert Hauser, M.D., Paul D. Feigin, Ph.D., Joseph Jankovic, M.D., Anthony Lang, M.D., William Langston, M.D., Eldad Melamed, M.D., Werner Poewe, M.D., Fabrizio Stocchi, M.D., and Eduardo Tolosa, M.D., for the ADAGIO Study Investigators*





PROLOPA

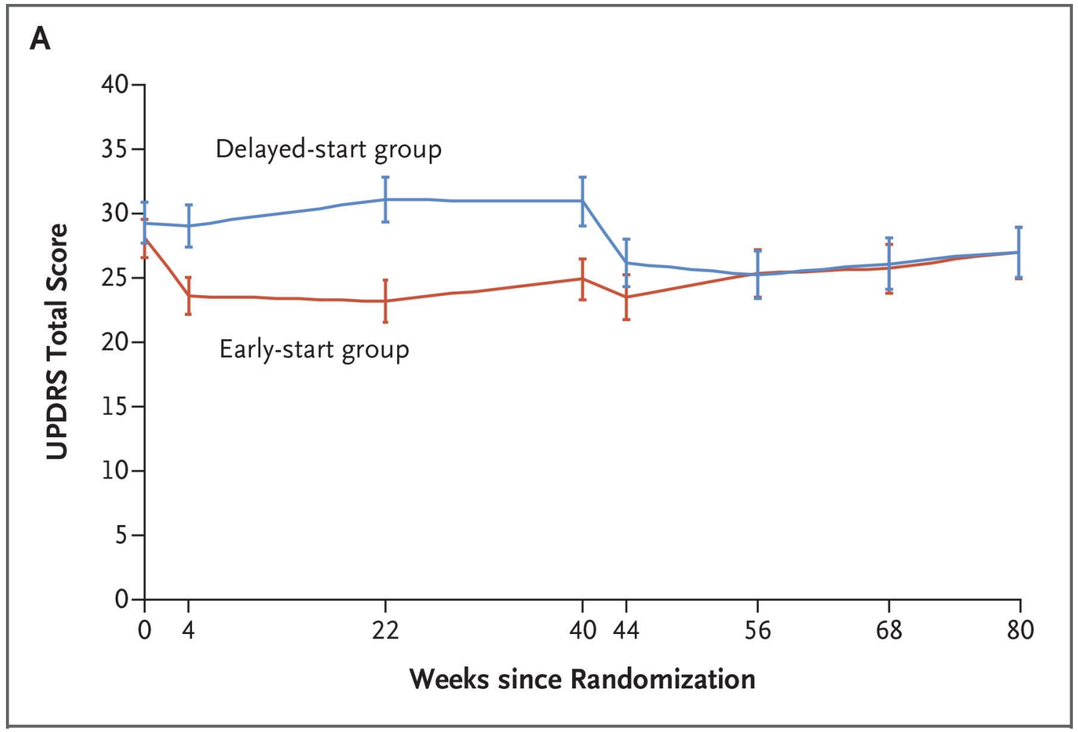
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 24, 2019 VOL. 380 NO. 4

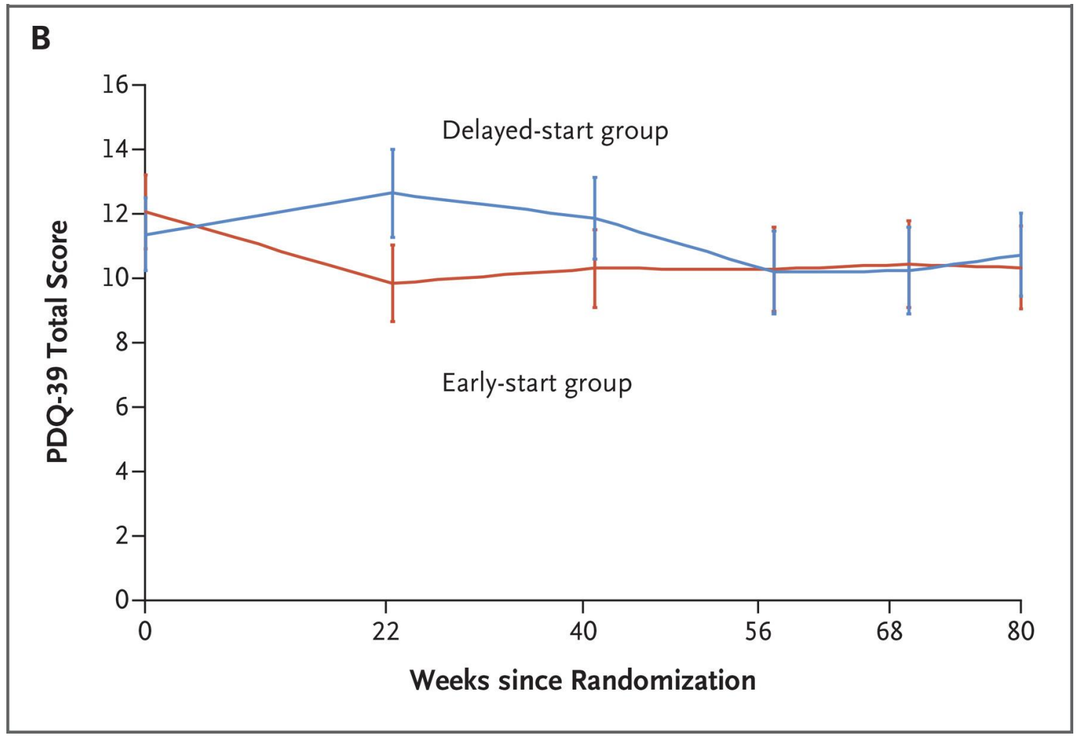
Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

C.V.M. Verschuur, S.R. Suwijn, J.A. Boel, B. Post, B.R. Bloem, J.J. van Hilten, T. van Laar, G. Tissingh, A.G. Munts, G. Deuschl, A.E. Lang, M.G.W. Dijkgraaf, R.J. de Haan, and R.M.A. de Bie, for the LEAP Study Group*

- Geen disease modifying effect
- Ook géén negatief effect om Prolopa vroeg te starten.

  Uitstellen geeft dus geen voordeel op lange termijn.





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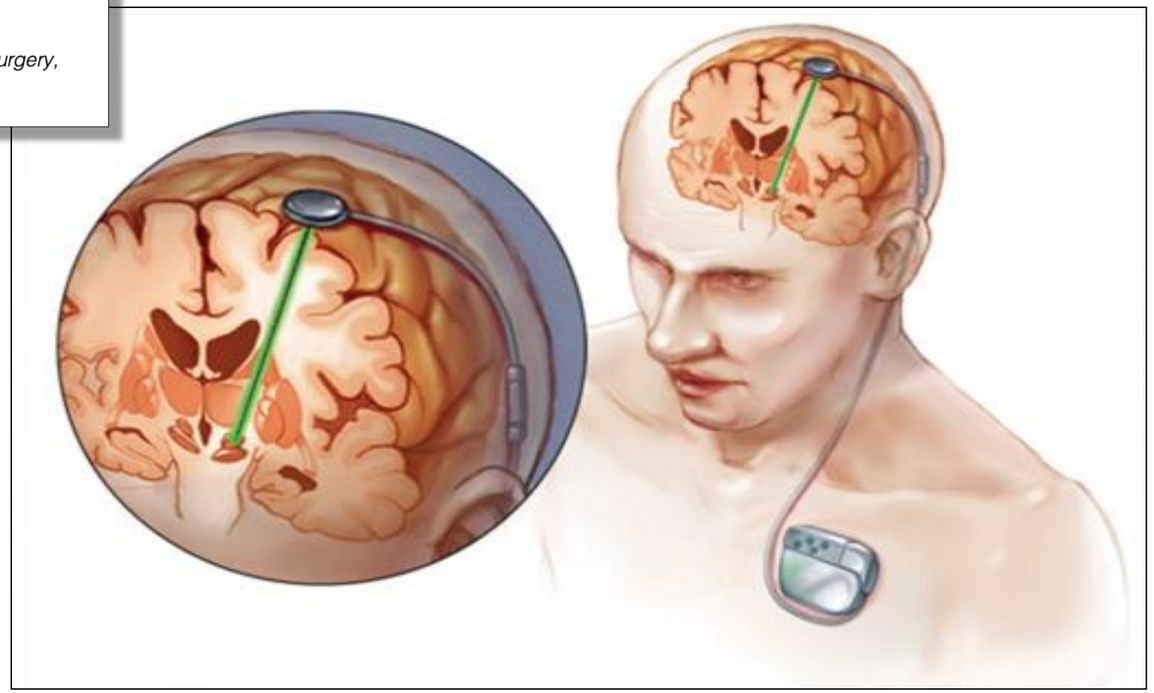
DIEPE HERSENSTIMULATIE

REVIEW

How Does Deep Brain Stimulation Change the Course of Parkinson's Disease?

Philipp Mahlknecht, MD, PhD,[1] Thomas Foltynie, MD, PhD,[2] Patricia Limousin, MD, PhD,[2] and Werner Poewe, MD[1*]

[1]*Department of Neurology, Innsbruck Medical University, Innsbruck, Austria*
[2]*Department of Clinical and Movement Neurosciences, UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, United Kingdom*



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ZIEKTEPROCES BEÏNVLOEDEN

- Op welke manier dit onderzoeken?

- Wat is het onderliggende ziekteproces?

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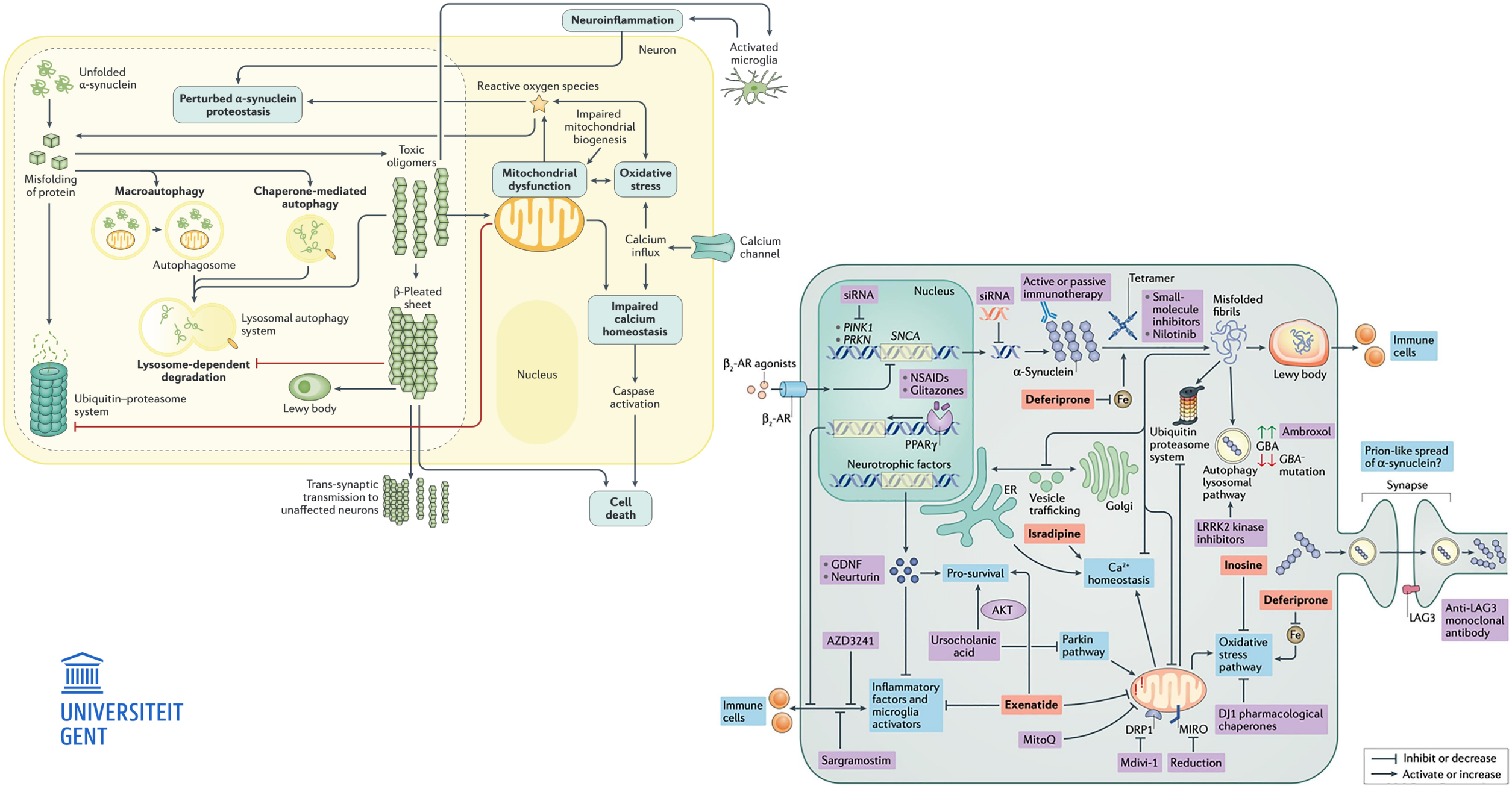
WAT MOETEN WE MODIFICEREN ?



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DISEASE MODIFYING THERAPIES

- Wat is een disease modifying behandeling?
  1. Ziekteproces stoppen (of vertragen)
     - a) Alfa-synucleïne
     - b) Genetische invalshoek (GBA, LRRK2)
     - c) Mitochondriaal
     - d) Autofagie
     - e) Inflammatie
     - f) Gastrointestinaal stelsel en microbioom
     - g) Ijzer chelatie

     Directe benadering

     Indirecte benadering

  2. Neuroprotectie
     (nog aanwezige neuronen beschermen)

  3. Reeds geleden schade herstellen
     (‘de klok terugdraaien’)

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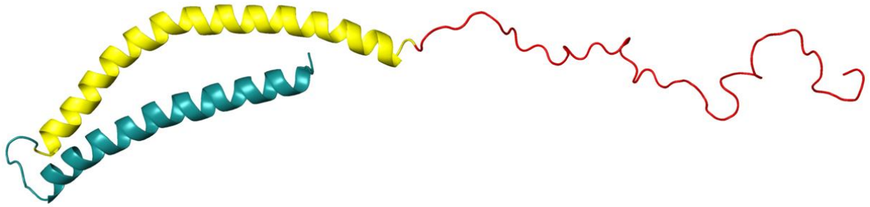
ALFA-SYNUCLEÏNE ALS DOELWIT



1. Verwijdering van extracellulair en mogelijk intracellulair eiwit
2. Blokkeren van de toxische effecten van alfa-synucleïne
3. Preventie van verspreiding van alfa-synucleïne van cel tot cel
4. Vermindering van inflammatie geïnduceerd door alfa-synucleïne

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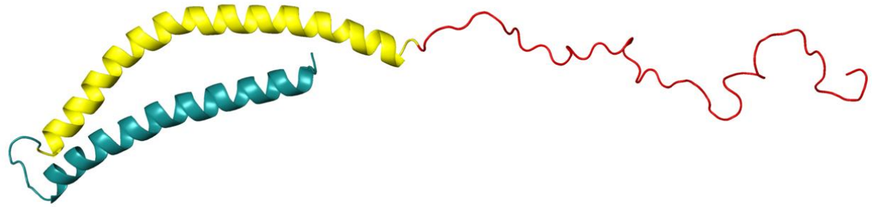
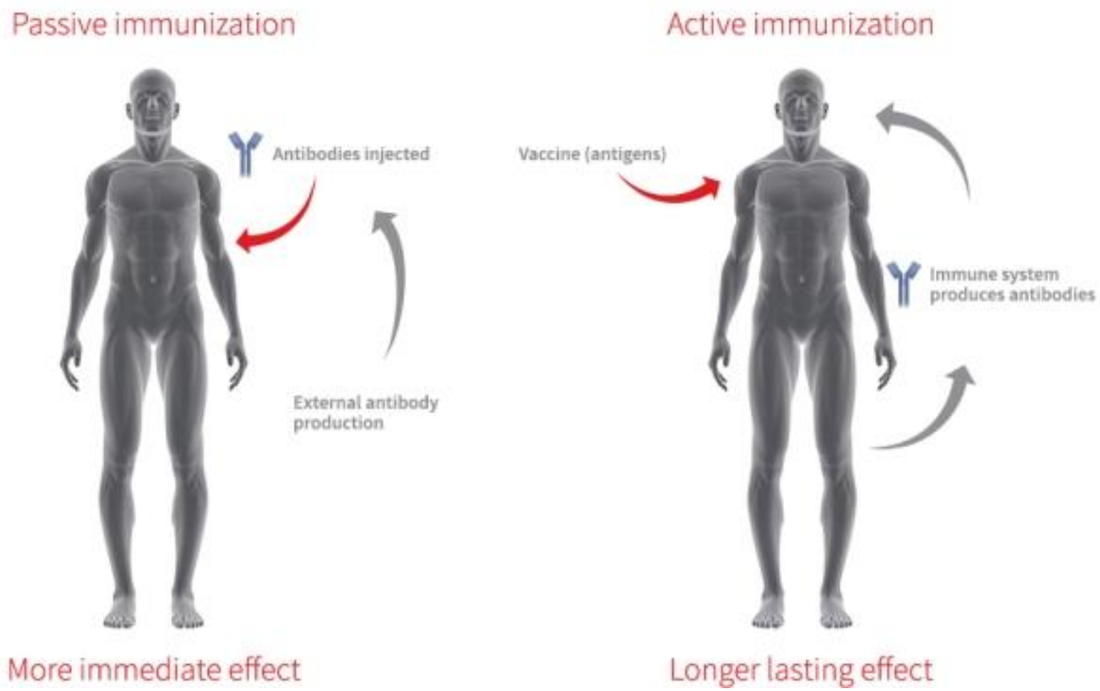
ALFA-SYNUCLEÏNE ALS DOELWIT

- Passieve immunotherapie
- Actieve immunotherapie
- Small molecules





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ALFA-SYNUCLEÏNE: PASSIEVE IMMUNOTHERAPIE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Prasinezumab in Early-Stage Parkinson's Disease

Gennaro Pagano, M.D., Ph.D., Kirsten I. Taylor, Ph.D., Judith Anzures-Cabrera, Ph.D., Maddalena Marchesi, M.D., Tanya Simuni, M.D., Kenneth Marek, M.D., Ph.D., Ronald B. Postuma, M.D., Nicola Pavese, M.D., Ph.D., Fabrizio Stocchi, M.D., Ph.D., Jean-Philippe Azulay, Ph.D., Brit Mollenhauer, M.D., Lydia López-Manzanares, M.D., et al., for the PASADENA Investigators and Prasinezumab Study Group*

Roche prothena

Primary end-point: MDS-UPDRS

Secondary end-point: DaTscan

ORIGINAL ARTICLE

Trial of Cinpanemab in Early Parkinson's Disease

Anthony E. Lang, M.D., Andrew D. Siderowf, M.D., Eric A. Macklin, Ph.D., Werner Poewe, M.D., David J. Brooks, M.D., D.Sc., Hubert H. Fernandez, M.D., Olivier Rascol, M.D., Nir Giladi, M.D., Fabrizio Stocchi, M.D., Caroline M. Tanner, M.D., Ph.D., Ronald B. Postuma, M.D., David K. Simon, M.D., Ph.D., et al., for the SPARK Investigators*

Biogen

Primary end-point: MDS-UPDRS

Secondary end-point: DaTscan

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ALFA-SYNUCLEÏNE: PASSIEVE IMMUNOTHERAPIE

Bedrijf	Stadium	Antibody	Resultaten
Astrazeneca & Takeda Pharmaceutical	Phase I trial	**MEDI1341**	Eind 2022
Lundbeck & Genmab	Phase II trial	**Lu AF82422**	Begin 2023
AbbVie & BioArctic Neuroscience	Phase II trial	**ABBV-0805**	TBA
Novartis & UCB	Phase I trial	**UCB7853**	TBA
Sanofi & ABL Bio	Phase I trial	**ABL301**	TBA

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ALFA-SYNUCLEÏNE: PASSIEVE IMMUNOTHERAPIE

Bedrijf	Stadium	Antibody	Resultaten
Astrazeneca & Takeda Pharmaceutical	Phase I trial	**MEDI1341**	Eind 2022
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AbbVie & BioArctic Neuroscience	Phase II trial	**ABBV-0805**	TBA
Novartis & UCB	Phase I trial	**UCB7853**	TBA
Sanofi & ABL Bio	Phase I trial	**ABL301**	TBA
Denali Therapeutics	Preklinisch		
Promis neurosciences	Preklinisch		
Cognyxx	Preklinisch	**CGX208**	
AC Immune	Preklinisch		
ICB International	Preklinisch		
Alligator Bioscience & BioArtcic	Preklinisch		
DegenRX	Preklinisch		
Crossbeta Biosciences	Preklinisch		

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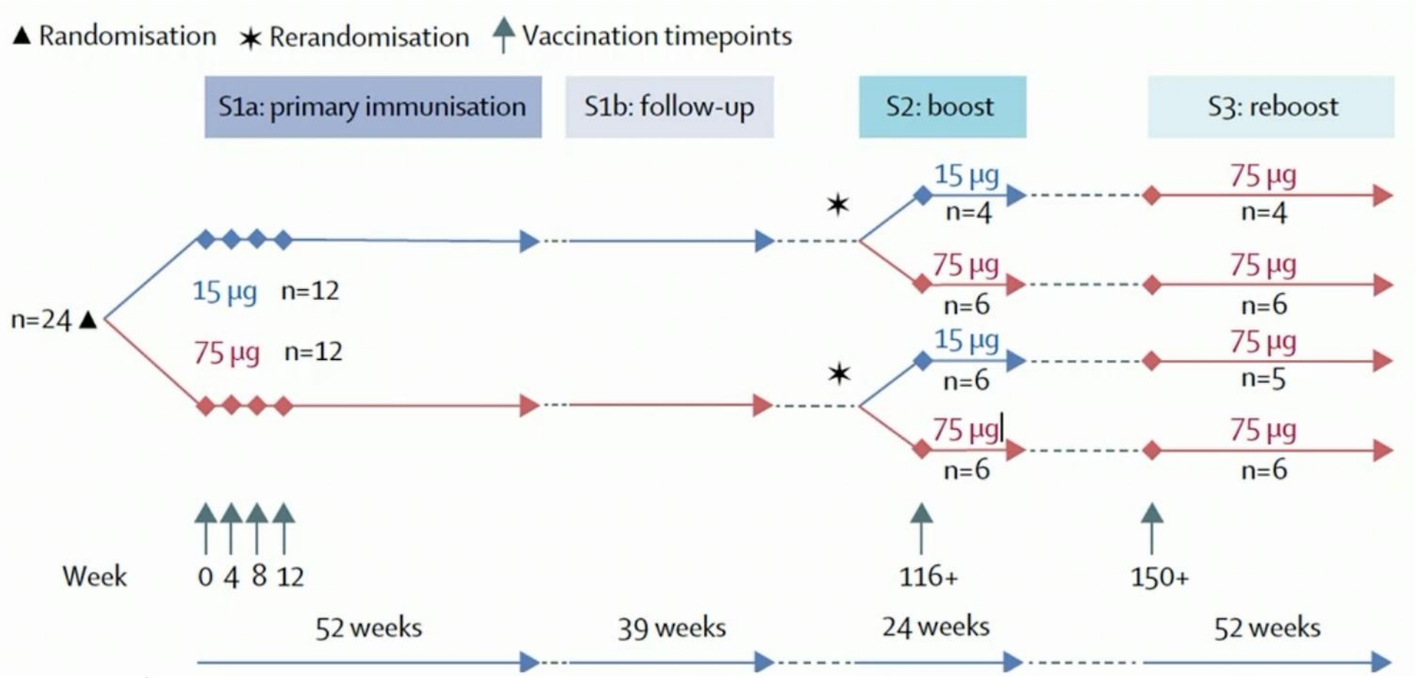
ALFA-SYNUCLEÏNE: ACTIEVE IMMUNOTHERAPIE

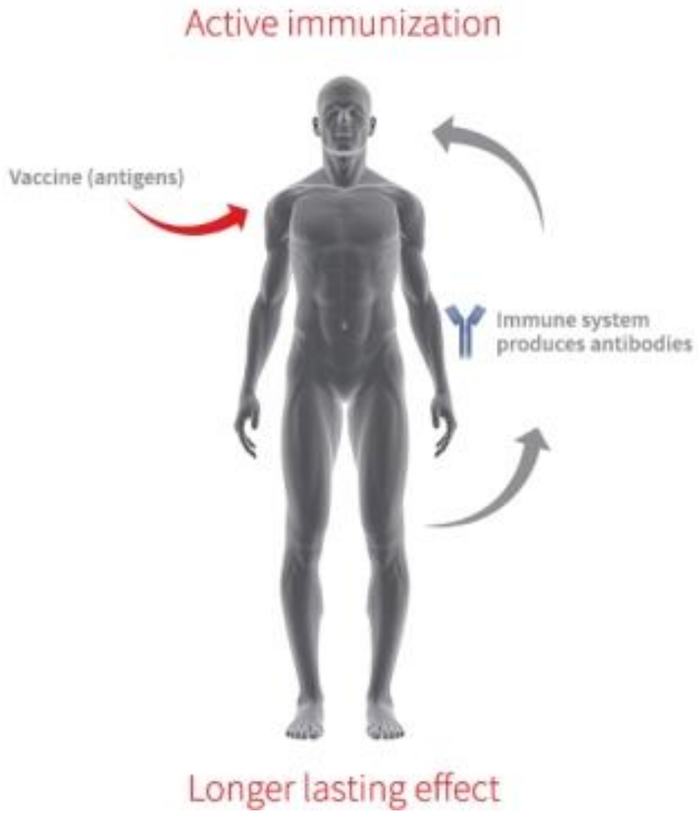
Safety and immunogenicity of the α-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial

Dieter Volc, Werner Poewe, Alexandra Kutzelnigg, Petra Lührs, Caroline Thun-Hohenstein, Achim Schneeberger, Gergana Galabova, Nour Majbour, Nishant Vaikath, Omar El-Agnaf, Dorian Winter, Eva Mihailovska, Andreas Maierhofer, Carsten Schwenke, Günther Staffler, Rossella Medori

AFFiRiS

AC Immune





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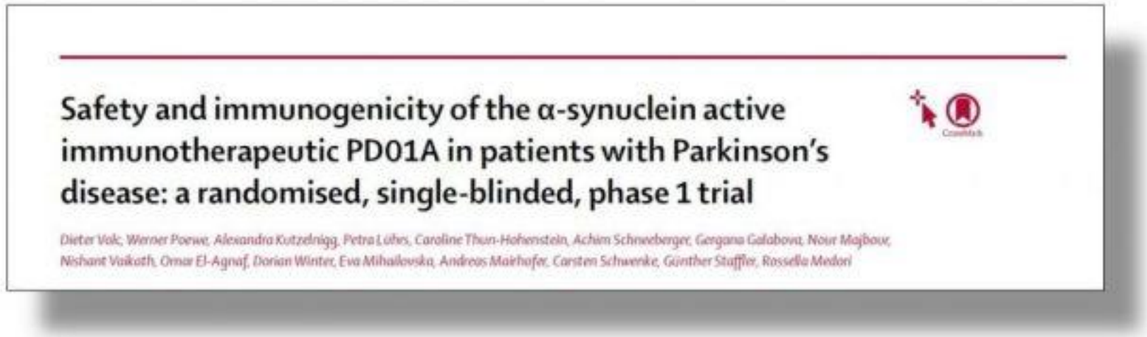
ALFA-SYNUCLEÏNE: ACTIEVE IMMUNOTHERAPIE



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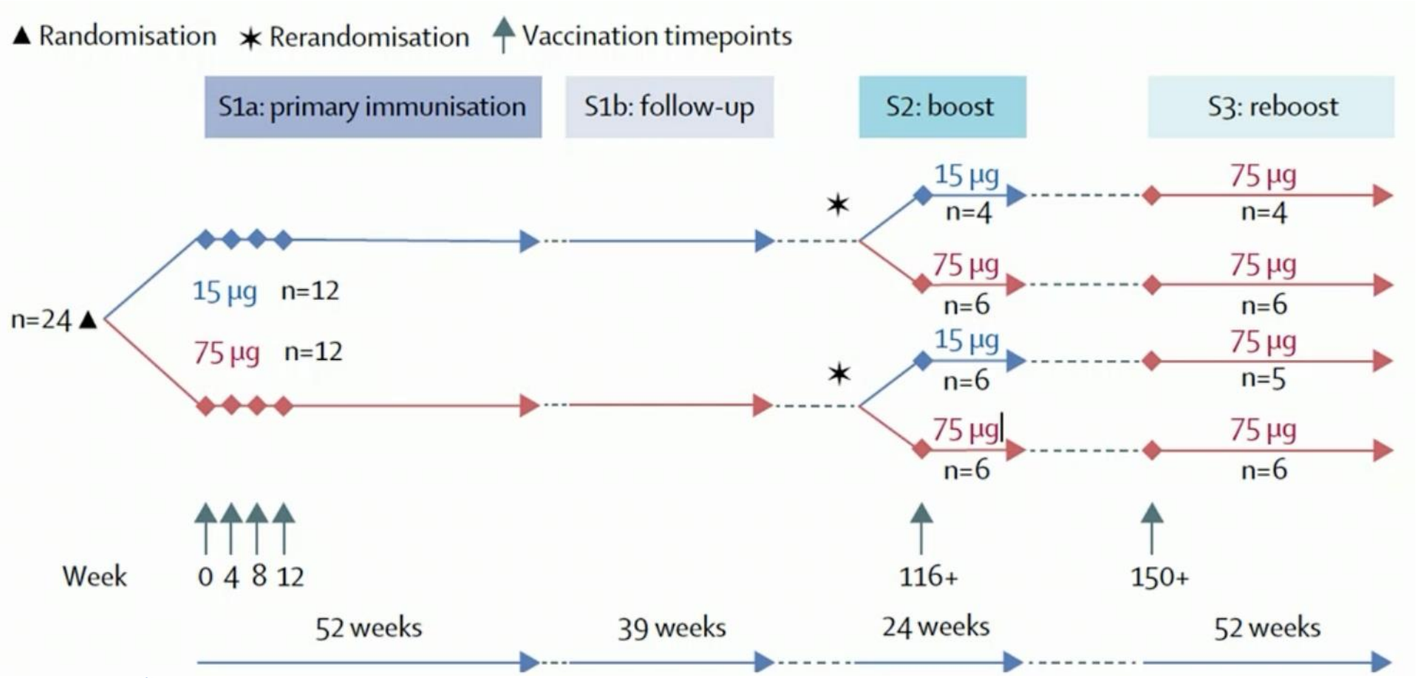

Open label studie (n = 24)

Resultaten phase I studie:

- Veilig en goed verdragen
- Productie van antilichamen (noodzaak van booster shots)
- 51% minder geaggregeerd alfa-synucleïne in CSF na 26 weken
- MDS-UPDRS: stabiel na 1 jaar
- DaTscan: stabiel na 1 jaar

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ALFA-SYNUCLEÏNE: ACTIEVE IMMUNOTHERAPIE

Bedrijf	Stadium	Antibody	Resultaten
Vaxxinity	Phase I	**UB-312**	December 2022
Capo Therapeutics	Preklinisch	**AV1947 - AV1950**	
Nuravax	Preklinisch	**PV-1950**	

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SMALL MOLECULES & ALFA-SYNUCLEÏNE

Bedrijf	Stadium	Small molecule alpha-synuclein inhibitors	Resultaten
ADepT-PD	Phase III (n = 408)	**Nortriptyline**	2023
Annovis	Phase III	**Buntanetap**	TBA
MODAG & Teva	Phase I	**Anle138b**	2022
Enterin	Phase II (n = 150)	**ENT-01**	2022
Yumanity	Phase II	**Stearoyl CoA desaturase (SCD) inhibitors**	TBA
Novartis & UCB	Phase II (n = 450)	**UCB0599**	July 2024
CliniCrowd	Phase II (n = 24)	**Mannitol**	2022
Priavoid	Preklinisch	**PRI-100**	
reMYND	Preklinisch	**ReS9 S and ReS 12S**	
Skyhawk	Preklinisch		
Nitrome Biosciences	Preklinisch	**Synuclein nitrases**	
Wren Therapeutics	Preklinisch		
TauRx	Preklinisch	G2-PD	

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SMALL MOLECULES & ALFA-SYNUCLEÏNE

Bedrijf	Stadium	Small molecule alpha-synuclein inhibitors	Resultaten
Priavoid	Preklinisch	**PRI-100**	
reMYND	Preklinisch	**ReS9 S and ReS 12S**	
Skyhawk	Preklinisch		
Nitrome Biosciences	Preklinisch	**Synuclein nitrases**	
Wren Therapeutics	Preklinisch		
TauRx	Preklinisch	**G2-PD**	
Gismo Therapeutics	Preklinisch	**GTC-5000**	
Fulcrum Therapeutics	Preklinisch		

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SMALL MOLECULES & ALFA-SYNUCLEÏNE

Bedrijf	Stadium	Small molecule alpha-synuclein inhibitors	Resultaten
Sangamo & Biogen	Preklinisch	**Gene therapy: ST-502**	
Prevail	Preklinisch	**Gene therapy: PR004**	
Seelos Therapeutics	Preklinisch	**Gene therapy: SLS-004**	
Neubase Therapeutics	Preklinisch	**Antisense oligonucleotides**	
nLife Therapeutics	Preklinisch	**Antisense oligonucleotides**	
Ionis Pharmaceuticals & Biogen	Preklinisch	**Antisense oligonucleotides**	
Osaka University	Preklinisch	**Antisense oligonucleotides**	
Alnylam Pharmaceuticals	Preklinisch	**Antisense oligonucleotides**	
Arvinas	Preklinisch	**Proteolysis targeting chimera**	
C4 Therapeutics & Biogen	Preklinisch	**Proteolysis targeting chimera**	
Primary Peptides	Preklinisch	**Proteolysis targeting chimera**	

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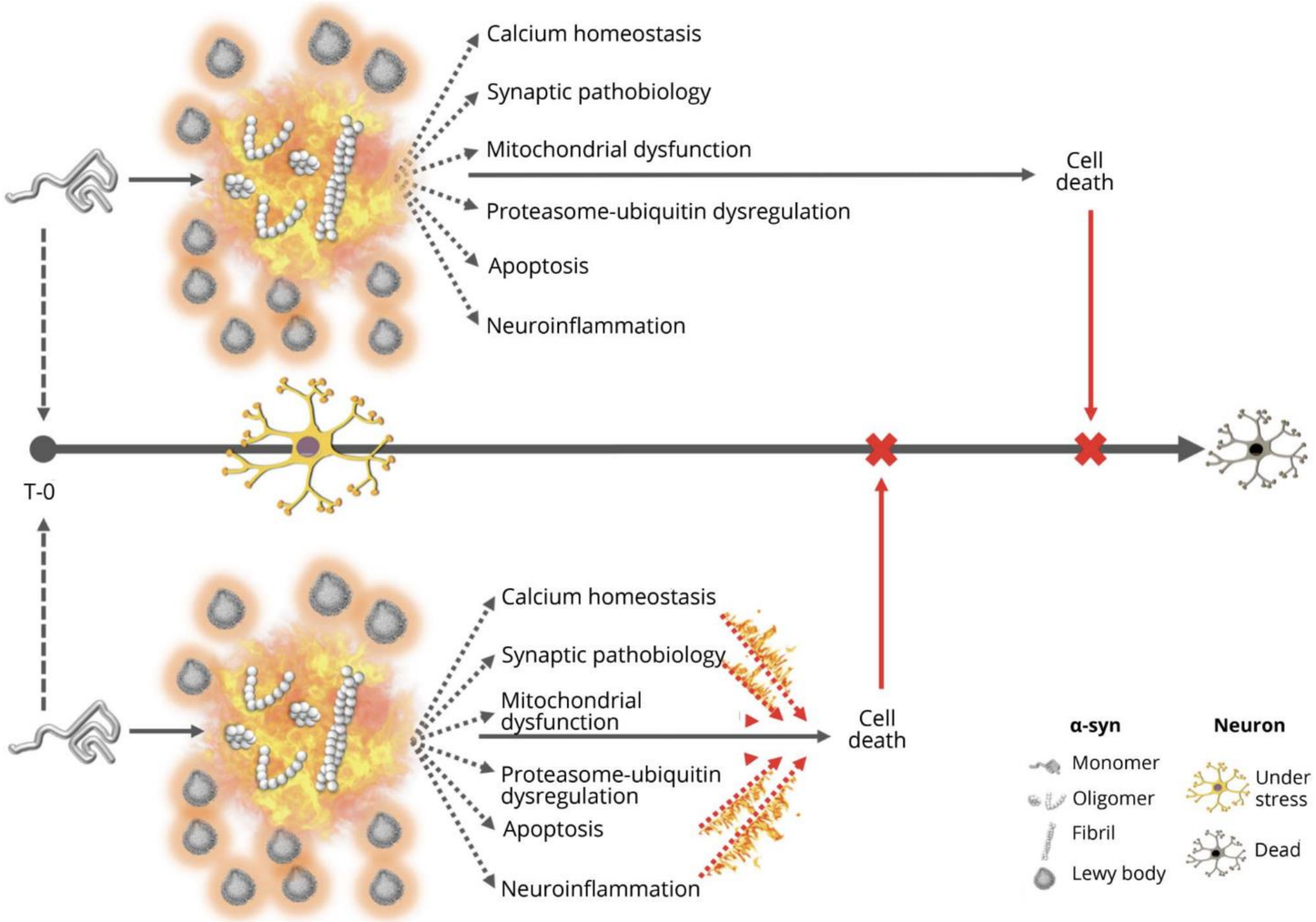
AMYLOID BETA IMMUNOTHERAPIE

Drug, year	Mechanism	Population	Phase	TE	Outcome
AN-1792, 2002	Aβ antigen	Mild-mod AD	2	Y	No change, toxic
Tramiprosate, 2007	Aβ aggregation inhibitor	Mild-mod AD	3	Y	No change
Tarenflurbil, 2009	γ-Secretase modulator	Mild AD	3	N	Worse globally
Scyllo-inositol, 2009	Aβ aggregation inhibitor	Mild-mod AD	2	Y	Increase mortality
Begacestat, 2010	γ-Secretase inhibitor	Mild-mod AD	2	N	No change, toxic
Ponezumab, 2011	Anti-Aβ antibody	Mild-mod AD	2	N	No change
Semagacestat, 2011	γ-Secretase inhibitor	Mild-mod AD	3	Y	Worse cognition, toxic
Bapineuzumab, 2012	Anti-Aβ antibody	Mild-mod AD	3	N	No change
Avagacestat, 2012	γ-Secretase inhibitor	Mild-mod AD	2	Y	Worse cognition
Avagacestat, 2012	γ-Secretase inhibitor	Prodromal AD	2	Y	Worse cognition, atrophy
Solanezumab, 2013	Anti-Aβ antibody	Mild-mod AD	3	Y	No change
Vanutide, 2013	Aβ antigen	Mild-mod AD	2	N	No change
Immunoglobulin, 2013	Anti-Aβ antibody	Mild-mod AD	3	N	No change
LY2886721, 2013	β-Secretase inhibitor	Mild-mod AD	2	Y	No change, toxic
AZD3839, 2013	β-Secretase inhibitor	Healthy	1	NR	Toxic; unpublished
Affitope AD02, 2014	Aβ antigen	Early AD	2	NR	Worse cognition
CAD106, 2014	Aβ antigen	Mild AD	2	Y	Worse cognition, atrophy
PBT2, 2014	Aβ aggregation inhibitor	Prodromal AD	2	N	No change
Crenezumab, 2014	Anti-Aβ antibody	Mild-mod AD	2	Y	No change
Gantenerumab, 2014	Anti-Aβ antibody	Prodromal AD	2	Y	No change
Gantenerumab, 2014	Anti-Aβ antibody	Mild AD	2	Y	No change
Solanezumab, 2016	Anti-Aβ antibody	Mild AD	3	Y	No change
Solanezumab, 2016	Anti-Aβ antibody	Prodromal AD	3	NR	Terminated, unpublished
Verubecestat, 2016	BACE inhibitor	Mild-mod AD	3	Y	Worse atrophy
Verubecestat, 2018	BACE inhibitor	Prodromal AD	3	Y	Worse cognition
Atabecestat, 2018	BACE inhibitor	Mild AD	3	Y	No change
Lanabecestat, 2018	BACE inhibitor	Mild AD	3	Y	Terminated, worse cognition
Crenezumab, 2018	Anti-Aβ antibody	Mild-mod AD	2	Y	No change
Solanezumab, 2018	Anti-Aβ antibody	Mild AD	3	N	No change
Verubecestat, 2018	BACE inhibitor	Mild-mod AD	3	Y	Worse cognition
Verubecestat, 2018	BACE inhibitor	Prodromal AD	3	Y	Worse cognition
Aducanumab, 2019 (2x)	Anti-Aβ antibody	Mild AD	3	Y	Benefit announced (1/2)
Lanabecestat, 2019 (2x)	BACE inhibitor	Mild AD	3	Y	No change (2/2)

AD: Alzheimer's disease. Aβ: beta-amyloid. NR: not reported. TE: target engagement.

PROTEIN AGGREGATION

Figure 2 Current model of protein aggregation in Parkinson disease (single disease model)



Abnormal soluble oligomers and fibrils of α-synuclein are directly pathogenic (upper panel). Alternatively or complementarily, secondary molecular changes created after protein aggregation combine with oligomers and fibrils to hasten cell death (lower panel). T-0 = time zero; α-syn = α-synuclein.

MEDICAL HYPOTHESIS

Revisiting protein aggregation as pathogenic in sporadic Parkinson and Alzheimer diseases

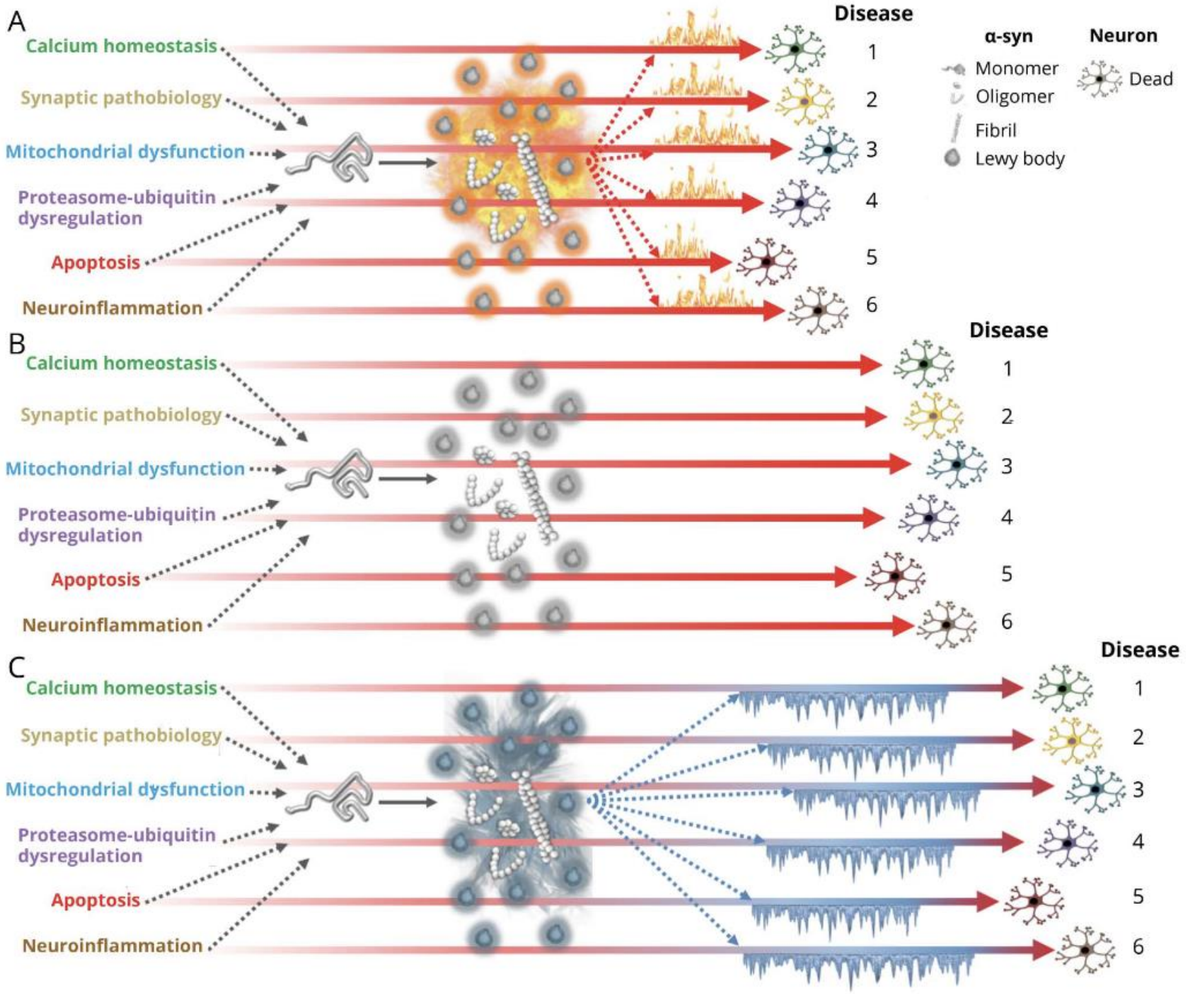
Alberto J. Espay, MD, MSc, Joaquin A. Vizcarra, MD, Luca Marsili, MD, PhD, Anthony E. Lang, MD, FRCPC, David K. Simon, MD, PhD, Aristide Merola, MD, PhD, Keith A. Josephs, MD, MST, MSc, Alfonso Fasano, MD, PhD, Francesca Morgante, MD, PhD, Rodolfo Savica, MD, MSc, J. Timothy Greenamyre, MD, PhD, Franca Cambi, MD, PhD, Tritia R. Yamasaki, MD, PhD, Caroline M. Tanner, MD, PhD, Ziv Gan-Or, MD, PhD, Irene Litvan, MD, Ignacio F. Mata, PhD, Cyrus P. Zabetian, MD, MS, Patrik Brundin, MD, PhD, Hubert H. Fernandez, MD, David G. Standaert, MD, PhD, Marcelo A. Kauffman, MD, PhD, Michael A. Schwarzschild, MD, PhD, S. Pablo Sardi, PharmD, PhD, Todd Sherer, PhD, George Perry, PhD, and James B. Leverenz, MD

Correspondence
Dr. Espay
alberto.espay@uc.edu

Neurology® 2019;92:329-337. doi:10.1212/WNL.0000000000006926

PROTEIN AGGREGATION

Figure 3 Alternative models of protein aggregation in Parkinson disease (multiple disease model)



Abnormal soluble oligomers and fibrils of α-synuclein (α-syn), while not directly pathogenic, act as accelerators of neurodegeneration ("fueling the fire") due to early pathogenic molecular abnormalities, each representing molecularly distinct diseases (A, model 1). Alternatively, abnormal soluble oligomers and fibrils of α-synuclein aggregate into Lewy bodies as byproducts of earlier pathogenic molecular mechanisms, without directly affecting the neurodegenerative process brought on by each molecular disease (B, model 2). Finally, α-synuclein aggregates into Lewy bodies as a mechanism to protect the neuron from toxic protein species or from the biological dysfunction that may have generated the formation of toxic species, "cooling" progression of cell degeneration under biological stress (C, model 3). Note that each molecularly defined disease has a different time to death; collectively, time to neuronal death is longest in diseases corresponding to model C.

MEDICAL HYPOTHESIS

Revisiting protein aggregation as pathogenic in sporadic Parkinson and Alzheimer diseases

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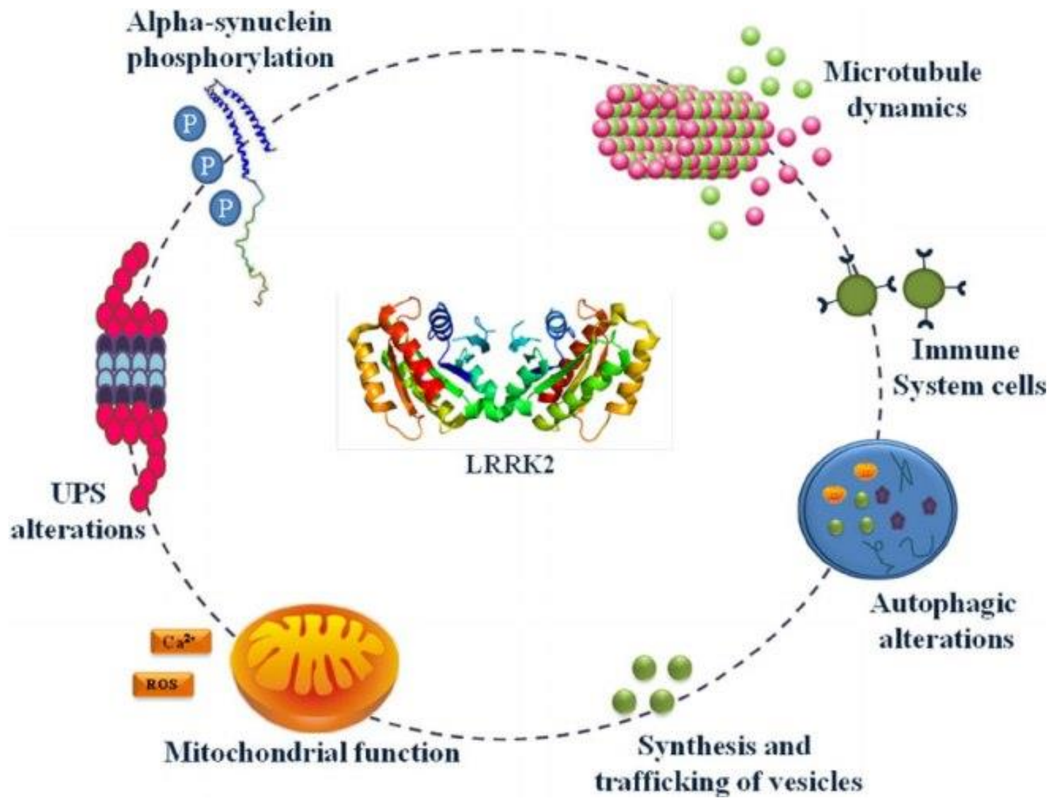
GENETISCHE INVALSHOEK

- **LRRK2:** G2019S mutatie (autosomaal dominant)
  - Leucine-rich repeat kinase 2
  - Gain-of-function: ‘overactivatie’ van het enzyme



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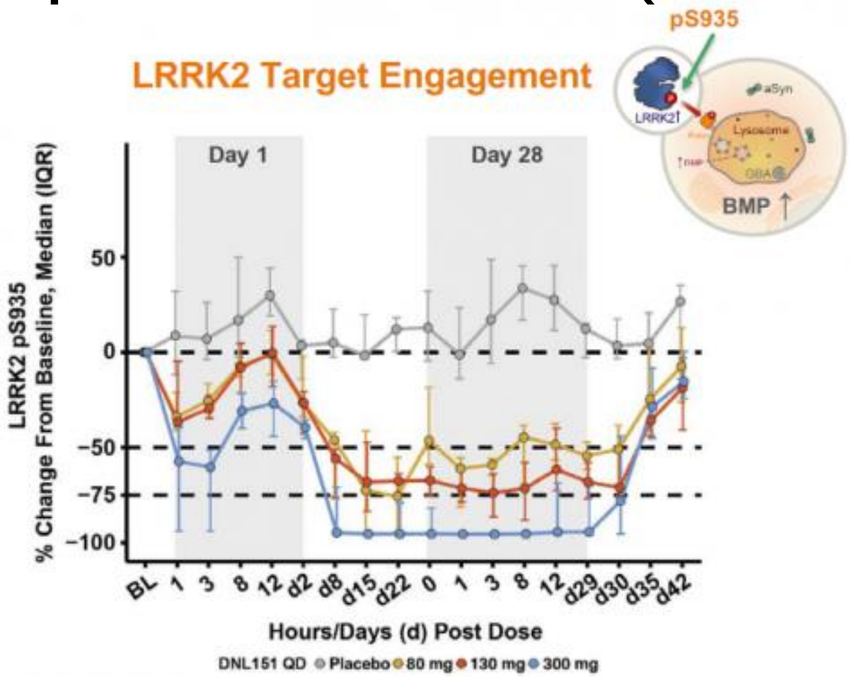
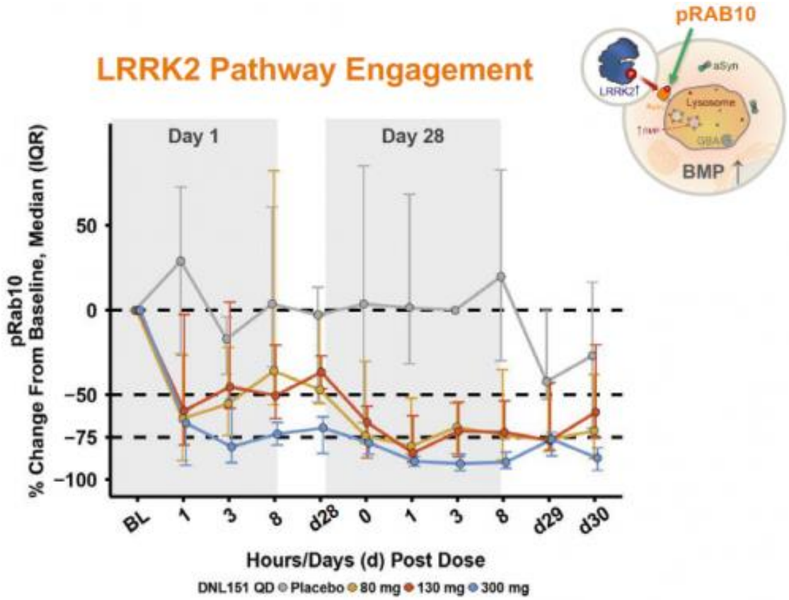
LRRK2

– Twee phase I studies (n = 184): veilig en getolereerd





– Phase III studie (n = 400 Parkinson mét LRRK2 mutatie)
– Phase II studie (n = 640 Parkinson zonder LRRK2 mutatie))

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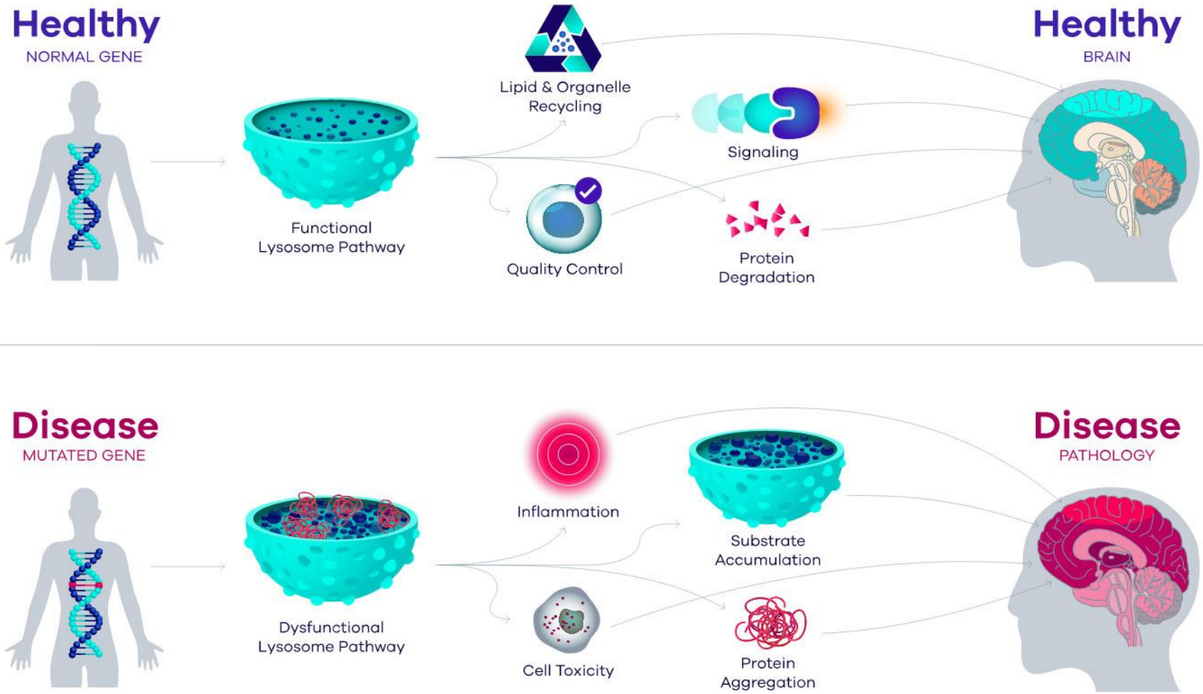
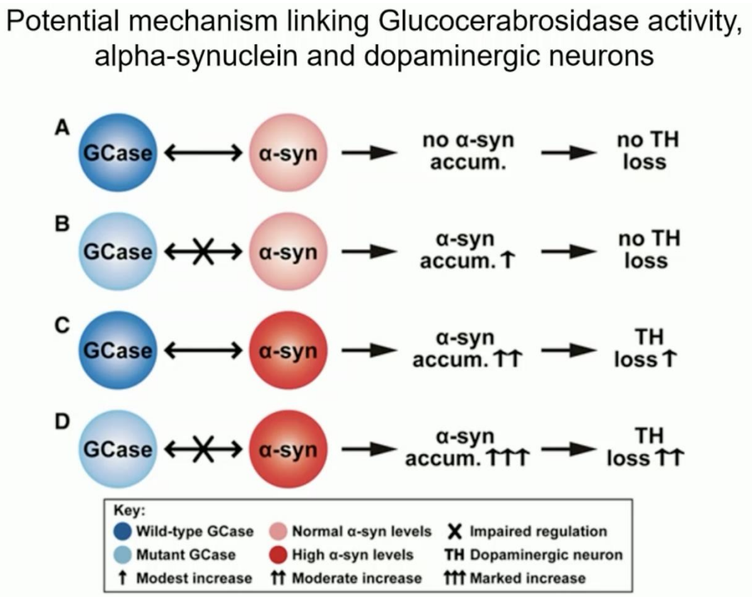
GENETISCHE INVALSHOEK

- **GBA** (genetische risicofactor)
  - Glucocerebrosidase
  - Loss-of-function





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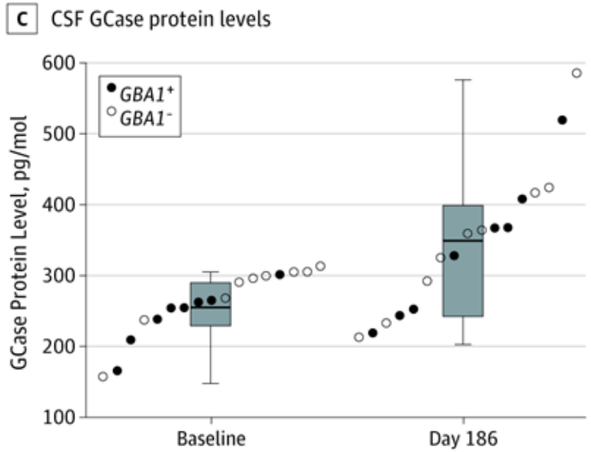
GBA

- Repurposed drug: **Ambroxol**



JAMA Neurology | Original Investigation

Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations
A Nonrandomized, Noncontrolled Trial

	Mean (SD)			
Result[a]	Baseline	Day 11	Day 93	Day 186
Total participants, No.				
Blood	18	18	18	18
CSF	17	17	17	17
Ambroxol, ng/mL				
Blood serum	0	316 (196)	1084 (396)	1432 (570)[b]
CSF	0	NA	NA	156 (53)[b]
GCase activity				
Blood leucocytes, nmol/mg/h	11.0 (5.2)	12.8 (4.9)	13.1 (4.8)	12.0 (5.2)
CSF, nmol/mL/h	0.309 (0.153)	NA	NA	0.250 (0.142)[b]
MDS-UPDRS score				
Part 3	31.1 (14.5)	NA	27.2 (10.7)	24.3 (12.1)[b]
Total	62.6 (32.2)	NA	57.7 (27.6)	53.9 (30.3)[b]

- Sanofi: **Venglustat**: Phase II: discontinued
- Andere compounds: Bial Biotech, Prevail, AVROBIO, Escape Bio, PTC Therapeutics, Biogen & Alectos Therapeutics, ...

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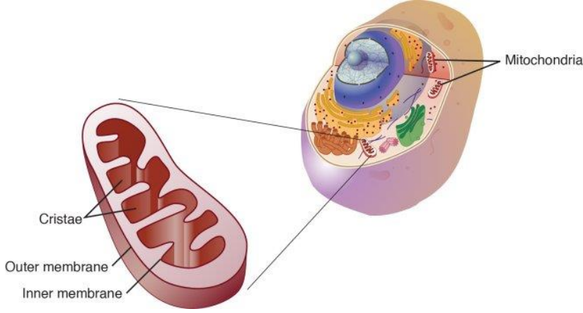
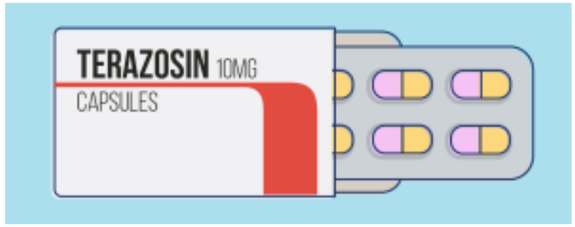
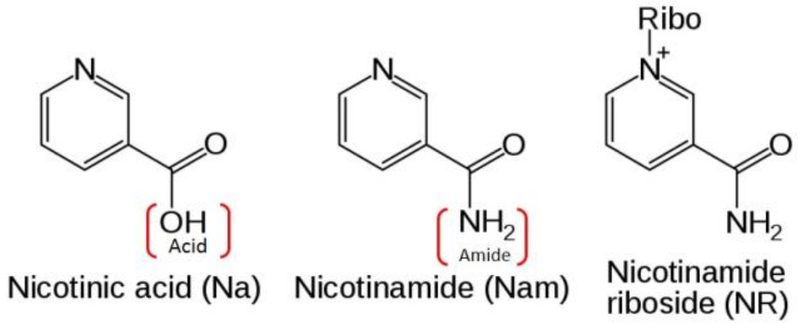
MITOCHONDRIAAL



- Repurposed drug: **UDCA** (Ursodeoxycholic acid)
- Repurposed drug: **Terazosine**



- **Nicotinamide Riboside** (Vitamin B3)



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DISEASE MODIFYING THERAPIES

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     c) Mitochondriaal
     d) Autofagie
     e) Inflammatie
     f) Gastrointestinaal stelsel en microbioom
     g) Ijzer chelatie

Directe benadering

Indirecte benadering

  2. Neuroprotectie
     (nog aanwezige neuronen beschermen)

  3. Reeds geleden schade herstellen
     (‘de klok terugdraaien’)

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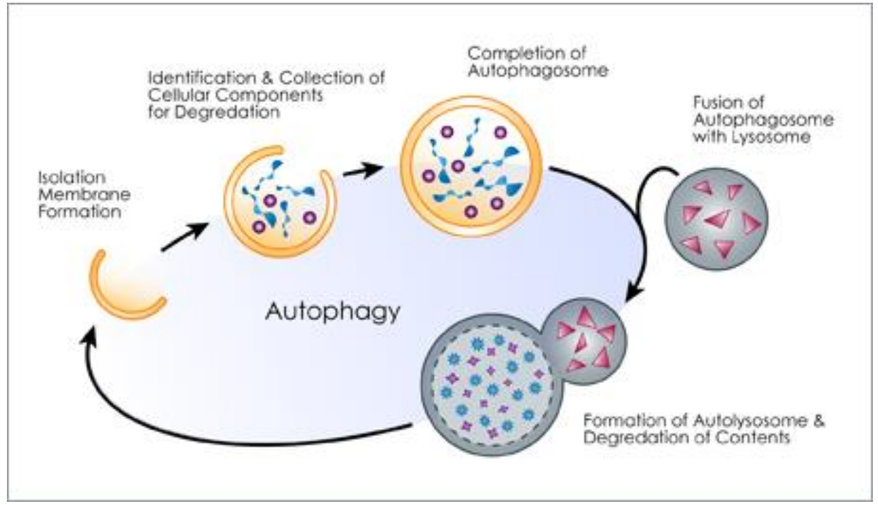
AUTOFAGIE



- Repurposed drugs: **c-Abl inhibitors**
  - **Nilotinib**: gefaald
  - **Brain-penetrant c-Abl inhibitors**
    - Vodobatinib, FB-101, Radotinib, IkT-148009

- Preklinisch:
  - **TORC1 inhibitoren**, **TRPML1-activating drugs**

INFLAMMATIE

- Repurposed drug: **Azathioprine** (immunosuppresief)
- **Xpro**: TNF inhibitor
- **Crisdesalazine:** prostaglandin E2 synthase-1 inhibitor
- **Sagramostim**: immunomodulatie
- **AKST4290**: CCR inhibitor
- **NE3107:** ERK inhibitor
- **NLRP3 inhibitors**: Inflammasoom


INFLAZOME
Targeted Therapies for Inflammatory Diseases

Inflazome announces acquisition by Roche

- Inflazome is a pioneering inflammasome company developing orally available NLRP3 inflammasome inhibitors to address clinical unmet needs across a wide variety of inflammatory diseases
- Acquisition of Inflazome gives Roche full rights to the Inflazome portfolio
- Activation of the NLRP3 inflammasome in the body is implicated in many diseases caused by chronic, uncontrolled inflammation
- Inflazome shareholders received €380 million upfront, and are eligible to receive additional milestone payments

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VERANDERDE SAMENSTELLING VAN DARMBACTERIËN BIJ DE ZIEKTE VAN PARKINSON


npj | Parkinson's Disease

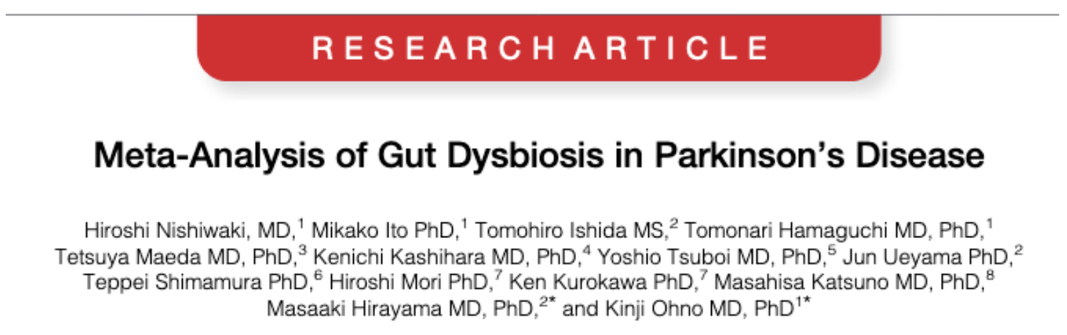
www.nature.com/npjparkd

ARTICLE OPEN

Check for updates

Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation

Stefano Romano[1✉], George M. Savva[1], Janis R. Bedarf[1,2], Ian G. Charles[1,3], Falk Hildebrand[1,4✉] and Arjan Narbad[1]


RESEARCH ARTICLE

Meta-Analysis of Gut Dysbiosis in Parkinson's Disease

Hiroshi Nishiwaki, MD,[1] Mikako Ito PhD,[1] Tomohiro Ishida MS,[2] Tomonari Hamaguchi MD, PhD,[1] Tetsuya Maeda MD, PhD,[3] Kenichi Kashihara MD, PhD,[4] Yoshio Tsuboi MD, PhD,[5] Jun Ueyama PhD,[2] Teppei Shimamura PhD,[6] Hiroshi Mori PhD,[7] Ken Kurokawa PhD,[7] Masahisa Katsuno MD, PhD,[8] Masaaki Hirayama MD, PhD,[2*] and Kinji Ohno MD, PhD[1*]

- Minder types bacteriën die kleine vetzuren produceren
  - **ontsteking**sremmende functie

- Meer types bacteriën die mucus op darmwand afbreken
  - negatieve invloed op de **darmwand** barrière

MICROBIOOM EN DE ZIEKTE VAN PARKINSON

- Verschillende **proefdierstudies** met veelbelovende resultaten.

- **Probiotica** studies

- **Antibiotica** studies

- **Stoelgangtransplantatie** studies

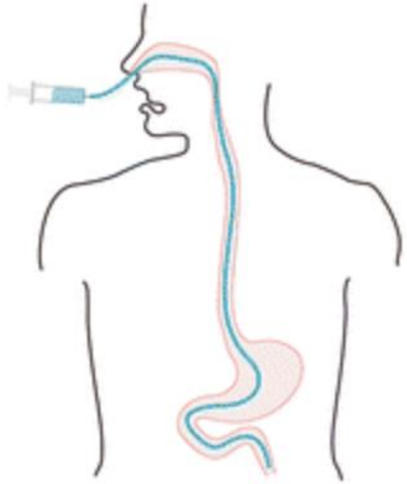
GUT-PARFECT

Prof. Dr. Patrick Santens

Prof. Dr. Debby Laukens

Prof. Dr. Roos Vandenbroucke

- **GUT-PARFECT: Double blind placebo-controlled randomized clinical trial**
  - 48 patiënten



- **Primary outcome:**

  MDS-UPDRS in OFF 1 year post-FMT

- **Resultaten verwacht begin 2023**

Studie-afspraak: screening

- Bevroren stoelgangstaal thuis verzamelen en meebrengen naar de studie-afspraak
- Vragenlijsten thuis invullen en meebrengen naar de studie-afspraak
- Klinisch onderzoek op een moment dat de medicatie is afgebouwd
- Bloeddruk, gewicht en lengte bepaling
- Bloedafname
- Verzameling van mondbacteriën en neusbacteriën via swabs, en speeksel en neusvocht.
- Bepaling van Prolopa (levodopa) concentratie in het bloed op verschillende tijdstippen
- Darmtransit bepaling door visualisatie van vooraf ingenomen time-markers via een röntgenfoto van de buik

Verzameling van vers stoelgangstaal dat verwerkt zal worden tot een transplant-oplossing

Coloscopie

FMT

FMT = Stoelgangtransplantatie

Van de eerste 5 ontlastingen na de stoelgangtransplantatie een staal invriezen (maar maximaal 1 staal verzamelen per dag)

Studie-afspraak op 3 maanden na de stoelgangtransplantatie.

Coloscopie op 3 maanden na de stoelgangtransplantatie.

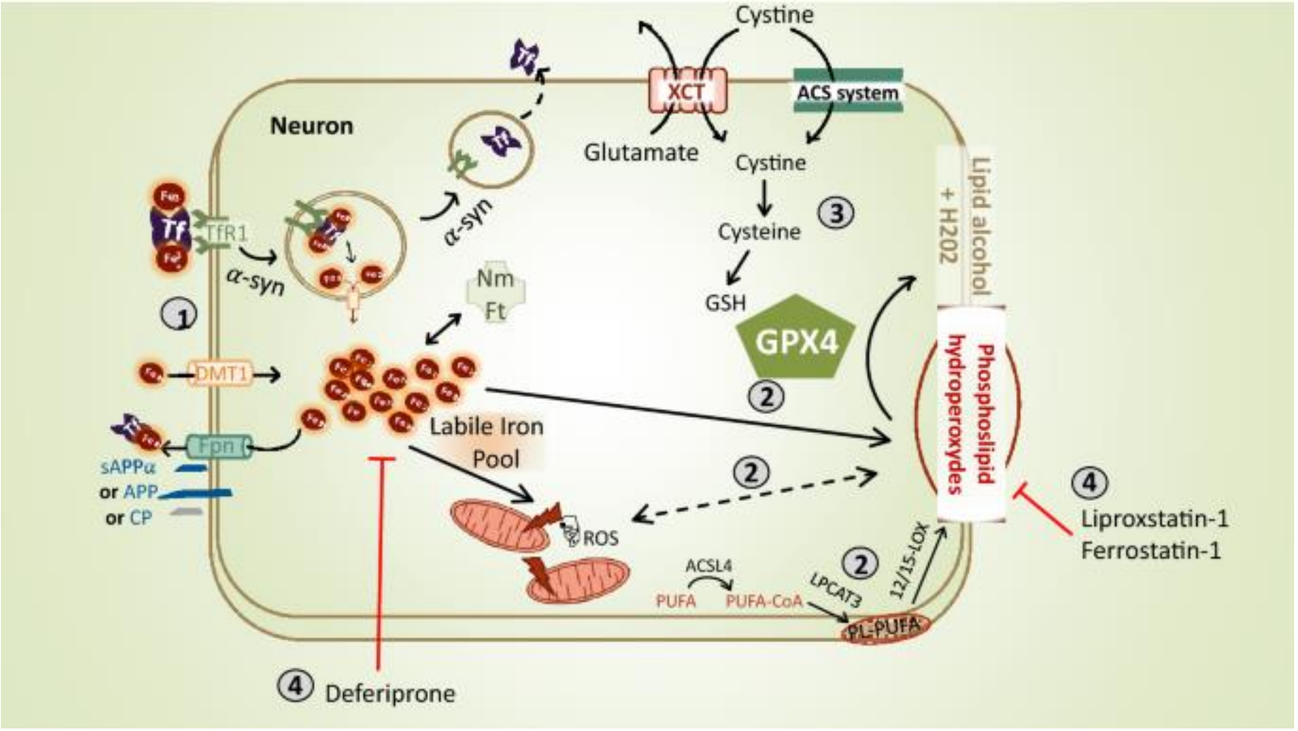
Studie-afspraak op 6 maanden na de stoelgangtransplantatie.

Studie-afspraak op 12 maanden na de stoelgangtransplantatie.

IJZER CHELATOREN

- **Deferiprone**
  - FAIRPARK II (n = 330)
  - SKY (n = 140)

- **ATH434**
  - Phase II lopende



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     e) Inflammatie
     f) Gastrointestinaal stelsel en microbioom
     g) Ijzer chelatie

     Directe benadering

     Indirecte benadering

  2. Neuroprotectie
     (nog aanwezige neuronen beschermen)

  3. Reeds geleden schade herstellen
     (‘de klok terugdraaien’)

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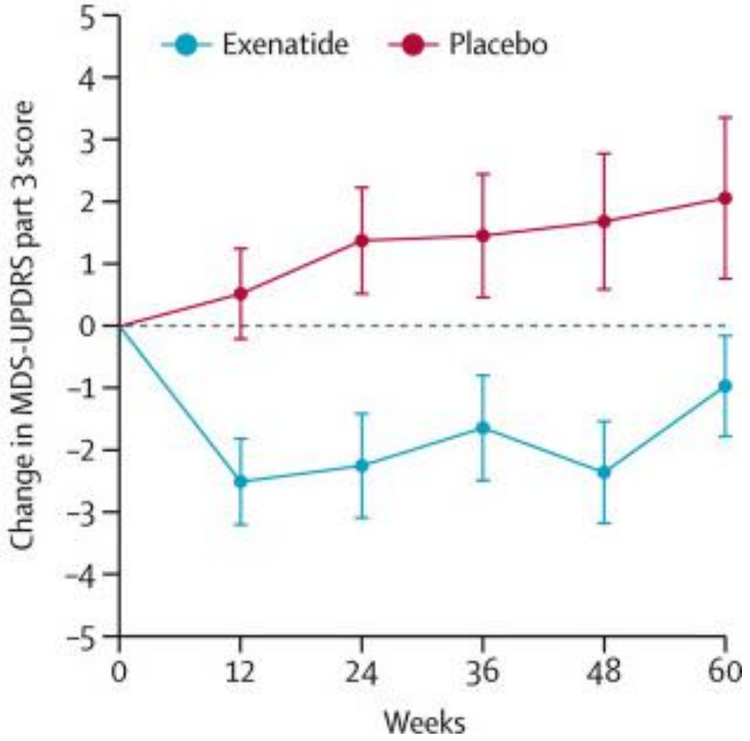
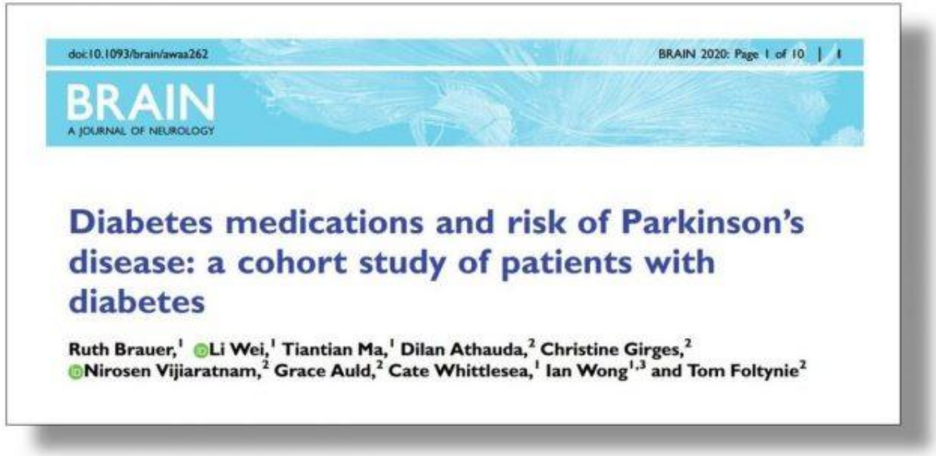
GLP-1R AGONISTEN

- Drug repurposing: **Exenatide**
  - Phase II studie
  - Phase III (n = 200) lopende
- **Lixisenatide**
- **Liraglutide**
- **Semaglutide**




doi:10.1093/brain/awaa262
BRAIN 2020: Page 1 of 10
BRAIN
A JOURNAL OF NEUROLOGY

Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes

Ruth Brauer,[1] Li Wei,[1] Tiantian Ma,[1] Dilan Athauda,[2] Christine Girges,[2] Nirosen Vijiaratnam,[2] Grace Auld,[2] Cate Whittlesea,[1] Ian Wong[1,3] and Tom Foltynie[2]

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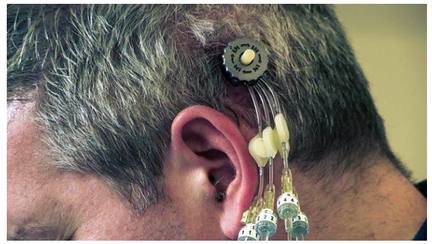
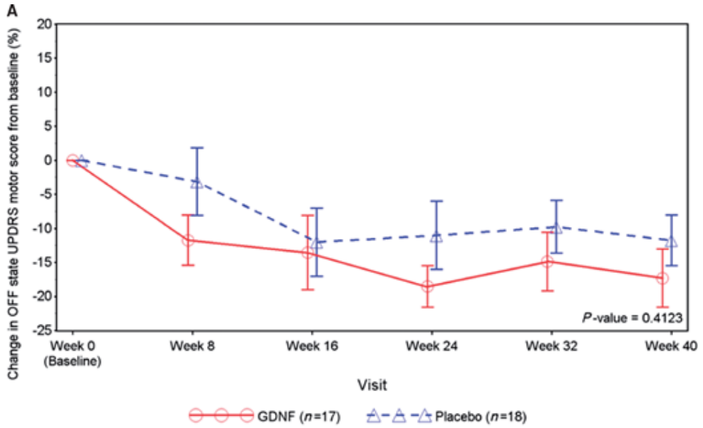
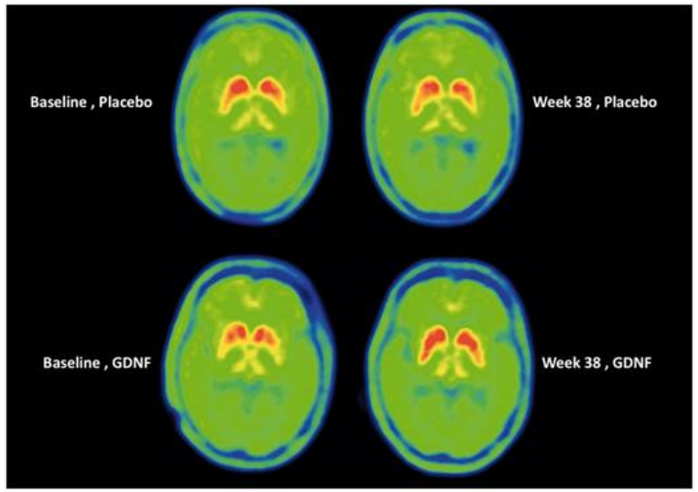
GDNF & CDNF

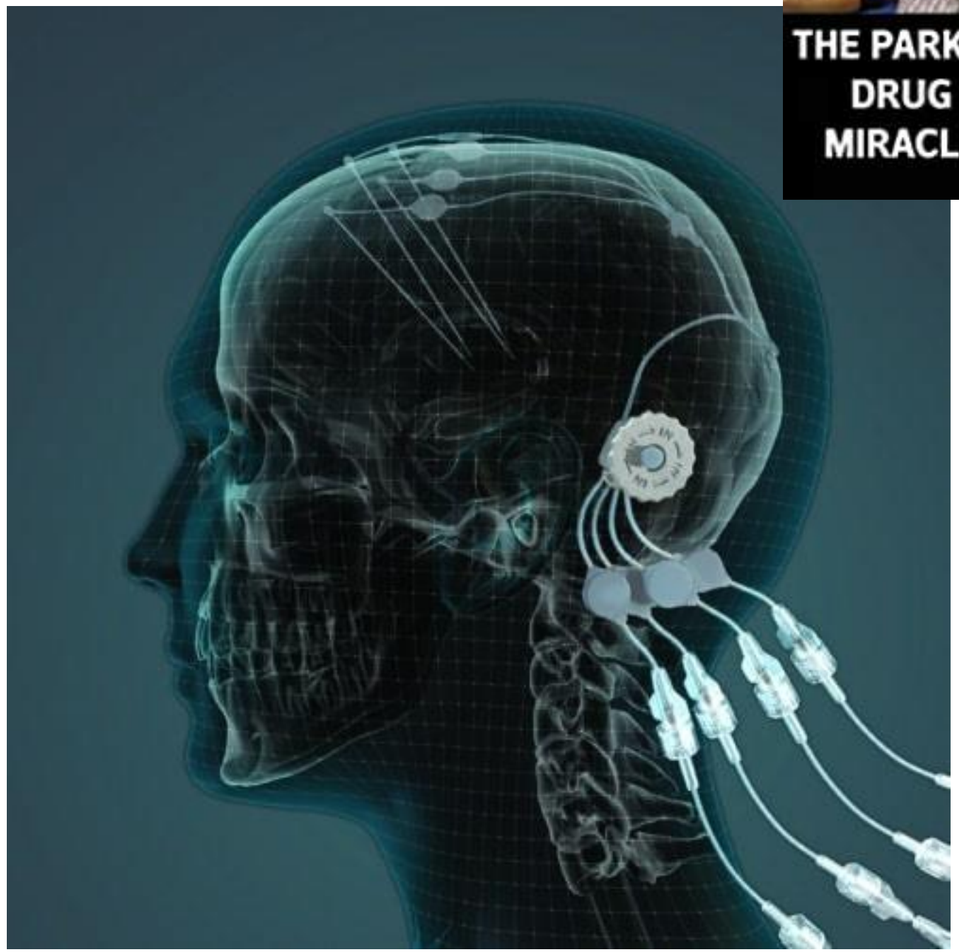
- Bristol Phase II **GDNF** clinical trial
  - Motorisch geen verschil




BRAIN
A JOURNAL OF NEUROLOGY
CLINICAL TRIAL
Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease







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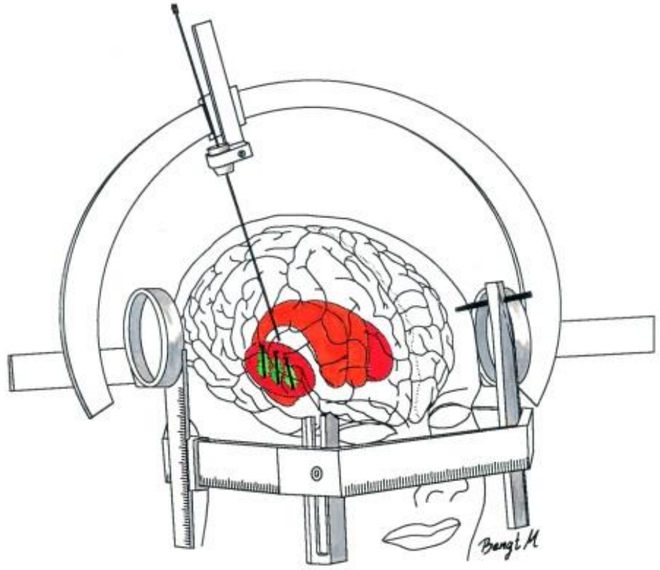
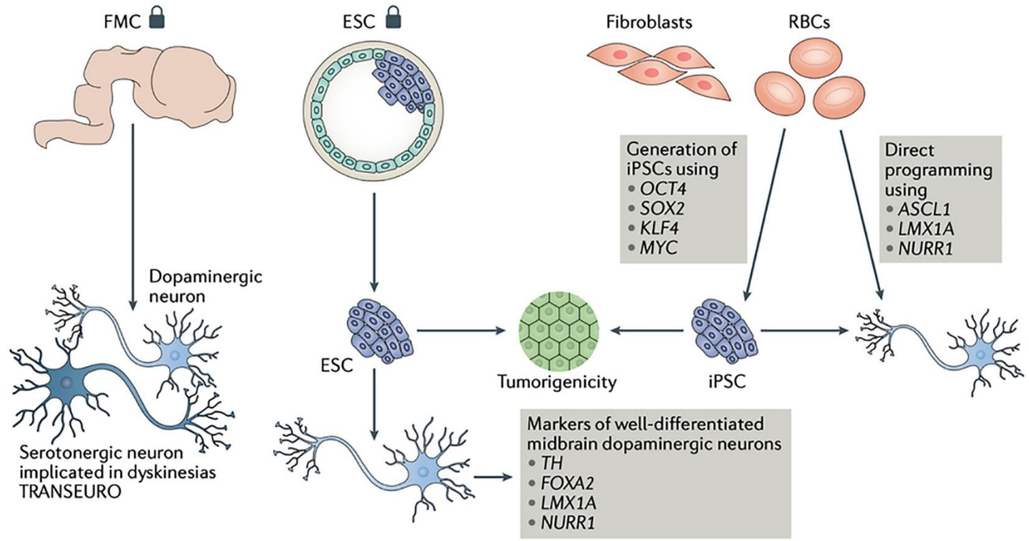
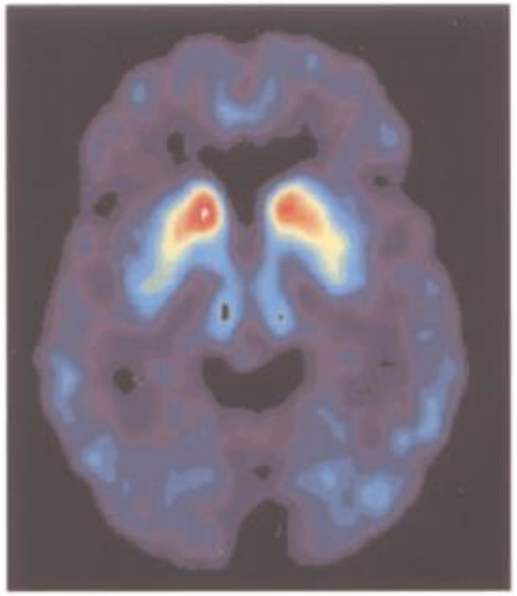
CEL TRANSPLANTATIE

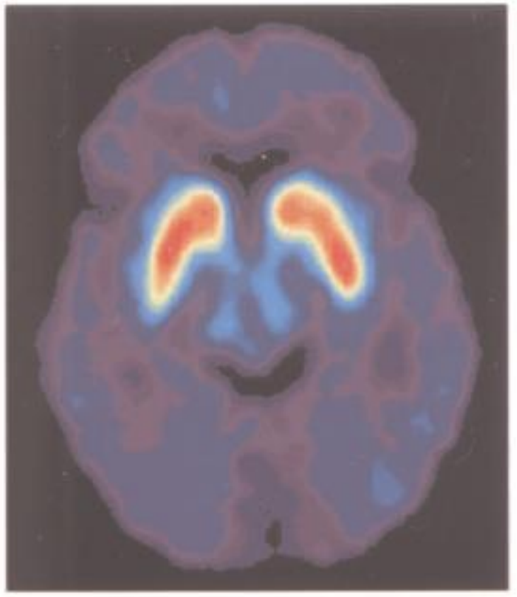
- TRANSEURO



- Kyoto cell transplantation trial
- China stem cell-based cell transplantation clinical trials







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VOEDING

- Retrospectieve studies: **mediterraan dieet** wordt geassocieerd met
  - lager risico op de ziekte van Parkinson (Alcalay et al., 2012)
  - oudere leeftijd bij diagnose (Metcalfe-Roach et al., 2021)
- Belang van vezels (SCFAs)

- Geen trials met dieet als behandeling in de ziekte van Parkinson

BEWEGING

RESEARCH ARTICLE OPEN ACCESS

Long-term Effect of Regular Physical Activity and Exercise Habits in Patients With Early Parkinson Disease

Kazuto Tsukita, MD, Haruhi Sakamaki-Tsukita, MD, and Ryosuke Takahashi, MD, PhD

Neurology® 2022;98:e859-e871. doi:10.1212/WNL.0000000000013218

Correspondence
Dr. Tsukita
kazusan@kuhp.kyoto-u.ac.jp

REVIEWS

Long-term effects of exercise and physical therapy in people with Parkinson disease

Margaret K. Mak[1], Irene S. Wong-Yu[1], Xia Shen[2] and Chloe L. Chung[1]

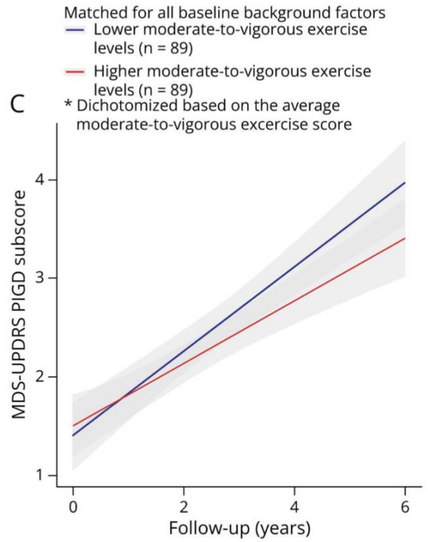
Research

JAMA Neurology | Original Investigation

Effect of High-Intensity Treadmill Exercise on Motor Symptoms in Patients With De Novo Parkinson Disease
A Phase 2 Randomized Clinical Trial

Margaret Schenkman, PhD, PT; Charity G. Moore, PhD; Wendy M. Kohrt, PhD; Deborah A. Hall, MD, PhD; Anthony DeLitto, PhD, PT; Cynthia L. Comella, MD; Deborah A. Josbeno, PT, PhD; Cory L. Christiansen, PhD, PT; Brian D. Berman, MD, MS; Benzi M. Kluger, MD; Edward L. Melanson, PhD; Samay Jain, MD; Julie A. Robichaud, BS-PT, MHS, PhD; Cynthia Poon, PhD; Daniel M. Corcos, PhD

- n = 237
- 5 jaar follow-up (observationele studie)
- **1-2x/week gedurende 1-2 uur** voldoende
- Geen associatie tussen baseline fysieke toestand en ziekte progressie = **nooit te laat om te starten**



EDITORIAL

Could Exercise Be the Answer?

Disease Modification With Long-term Regular Physical Activity in Parkinson Disease

Margaret K. Y. Mak, PhD, and Heidi Beck Schwarz, MD

Neurology® 2022;98:303-304. doi:10.1212/WNL.0000000000013208

Correspondence
Dr. Mak
margaret.mak@
polyu.edu.hk

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Bedankt voor uw aandacht