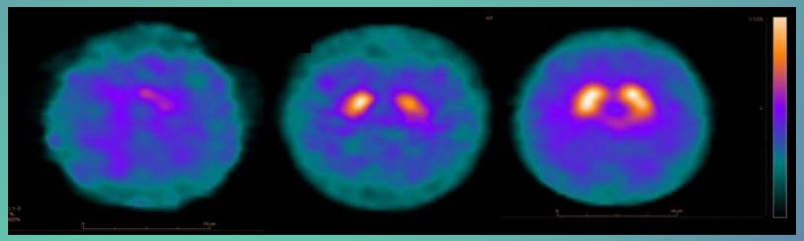
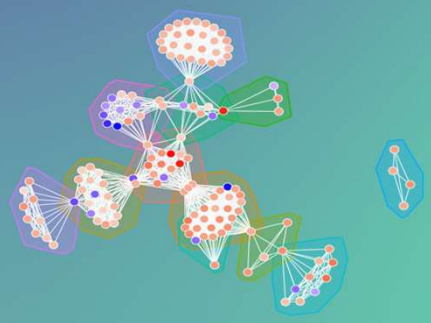
Neuro-SysMed

Parkinson's disease: from the patient the lab and back





Prof. Charalampos Tzoulis

Co-Director Neuro-SysMed Center

Haukeland University Hospital &

University of Bergen

Parkinson's disease: a major societal challenge

- ~2.5% of the population > 65 years
- ~5% of the population > 85 years
- Norway:
  - 2020: 8,000
- World
  - 2020: 10 million

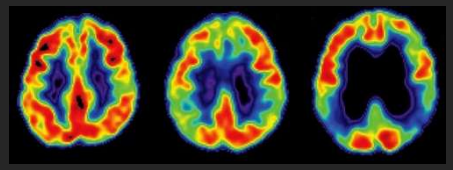
Treatments don’t work

- Clinicaltrials.gov for PD
  - 1162 trial completed
  - 0 have achieved a disease-modulating effect

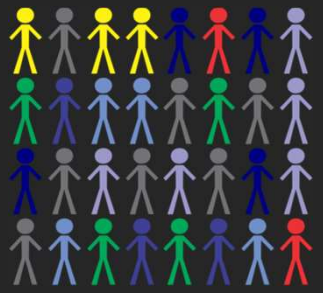
Key challenges in PD-research

Mechanisms

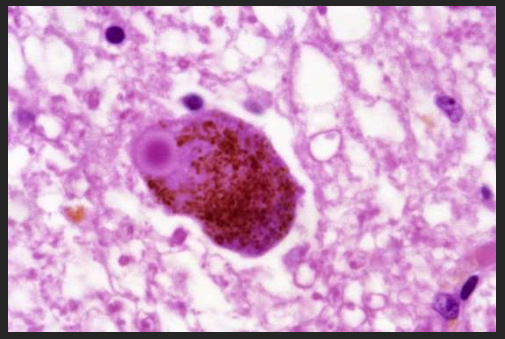
Disease models

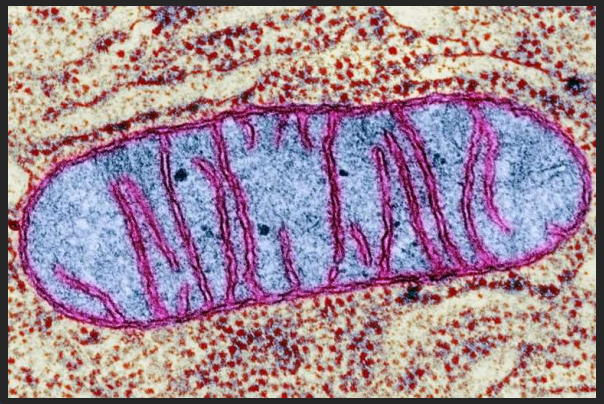


Heterogeneity



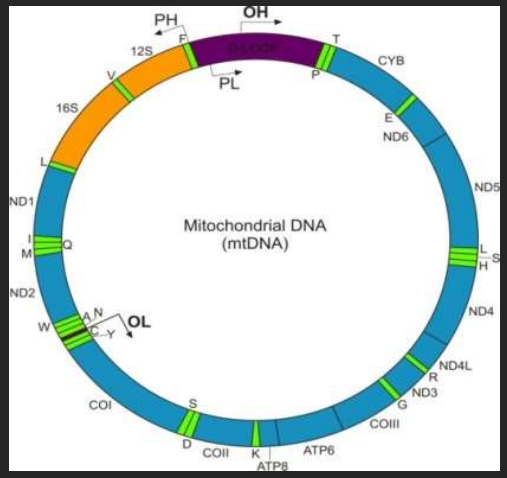
What is the cause of Parkinson's disease?

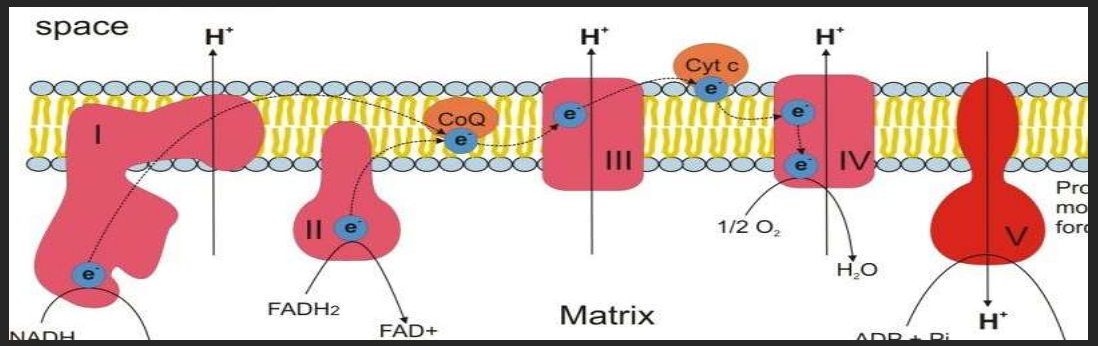




?

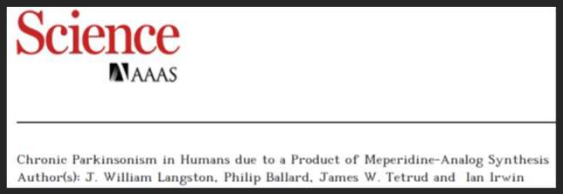
Mitochondria produce ATP





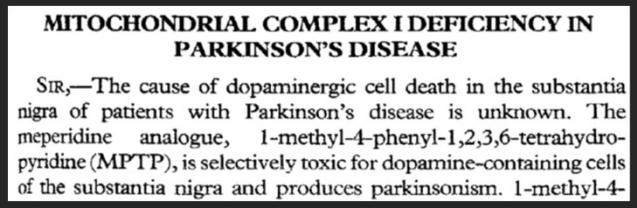
Respiratory chain

PD and mitochondria


Science
AAAS

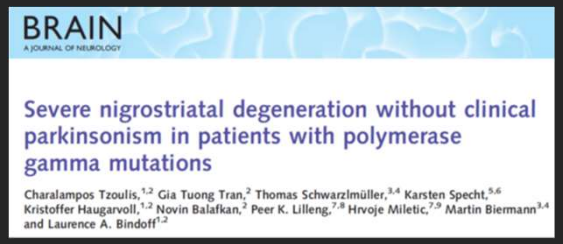
Chronic Parkinsonism in Humans due to a Product of Meperidine-Analog Synthesis
Author(s): J. William Langston, Philip Ballard, James W. Tetrud and Ian Irwin

Langston et al 1983


MITOCHONDRIAL COMPLEX I DEFICIENCY IN PARKINSON'S DISEASE

SIR,—The cause of dopaminergic cell death in the substantia nigra of patients with Parkinson's disease is unknown. The meperidine analogue, 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP), is selectively toxic for dopamine-containing cells of the substantia nigra and produces parkinsonism. 1-methyl-4-

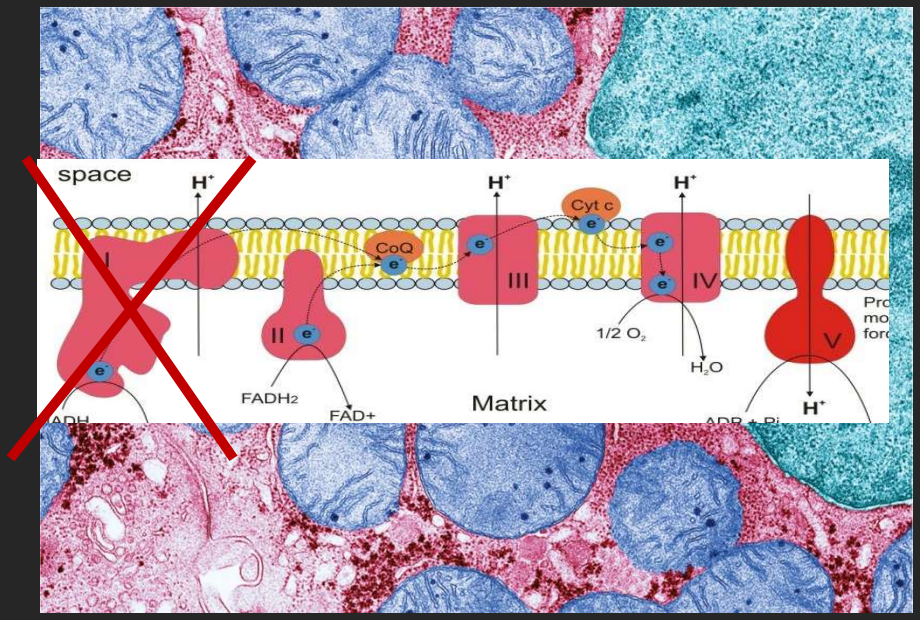
Schapira et al 1989


BRAIN
A JOURNAL OF NEUROLOGY

Severe nigrostriatal degeneration without clinical parkinsonism in patients with polymerase gamma mutations

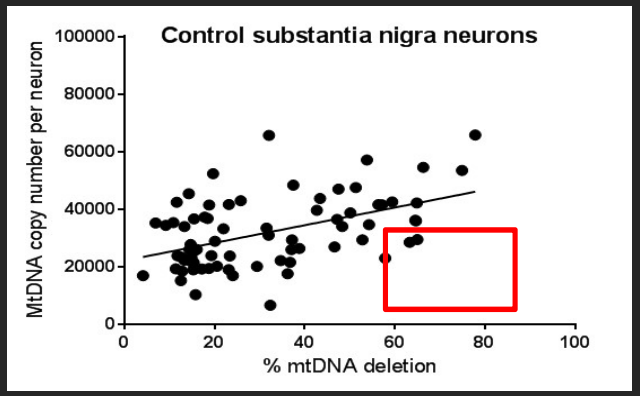
Charalampos Tzoulis,[1,2] Gia Tuong Tran,[2] Thomas Schwarzlmüller,[3,4] Karsten Specht,[5,6] Kristoffer Haugarvoll,[1,2] Novin Balafkan,[2] Peer K. Lilleng,[7,8] Hrvoje Miletic,[7,9] Martin Biermann[3,4] and Laurence A. Bindoff[1,2]

Tzoulis et al 2013

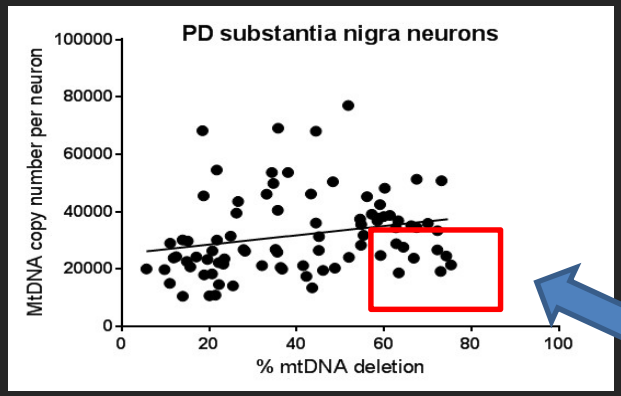


Mitochondrial homeostasis fails in PD

Controls



PD



Loss of healthy mtDNA

Christian Dölle

Irene Flønes

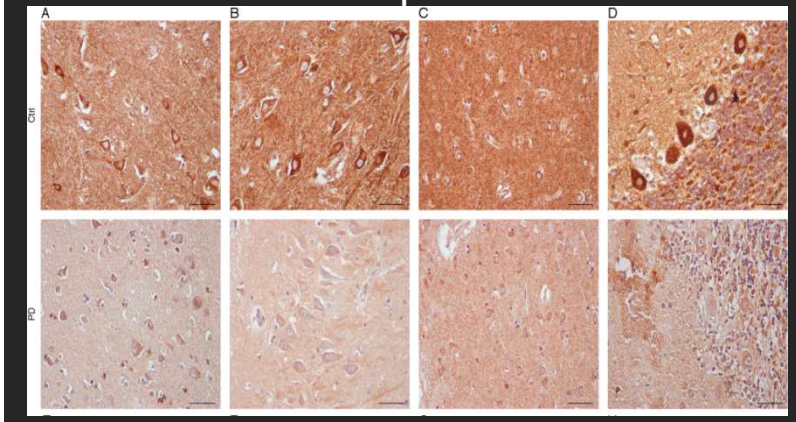
nature COMMUNICATIONS

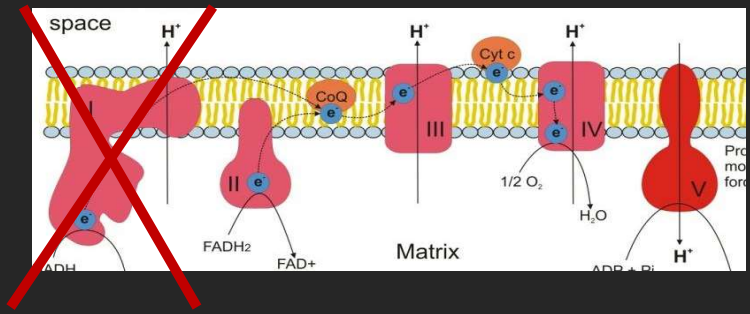
Defective mitochondrial DNA homeostasis in the dopaminergic substantia nigra of patients with Parkinson's disease

Gonzalo S. Nido

Global complex I deficiency in the PD brain

Complex I





Irene Fløtnes

Acta Neuropathologica (2018) 135:409–425
https://doi.org/10.1007/s00401-017-1794-7

ORIGINAL PAPER

CrossMark

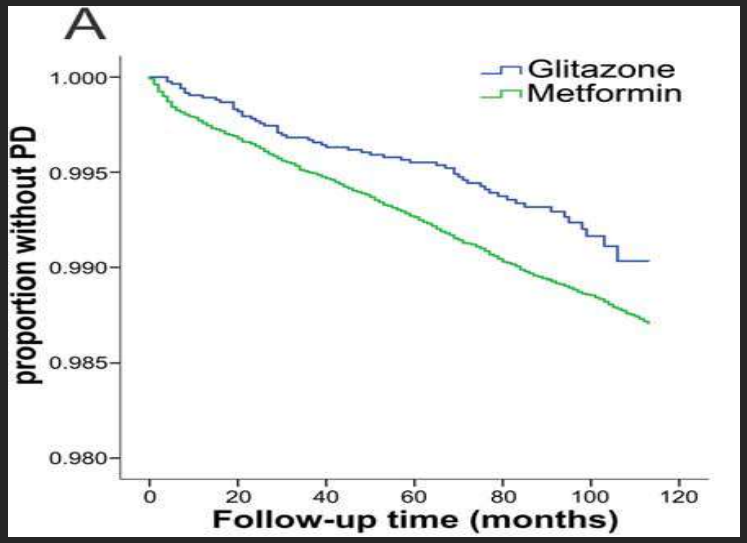
Neuronal complex I deficiency occurs throughout the Parkinson's disease brain, but is not associated with neurodegeneration or mitochondrial DNA damage

Irene H. Flønes[1,2] · Erika Fernandez-Vizarra[3] · Maria Lykouri[1,2] · Brage Brakedal[1,2] · Geir Olve Skeie[1,2] · Hrvoje Miletic[4,5] · Peer K. Lilleng[4,6] · Guido Alves[7,8] · Ole-Bjørn Tysnes[1,2] · Kristoffer Haugarvoll[1,2] · Christian Dölle[1,2] · Massimo Zeviani[3] · Charalampos Tzoulis[1,2]

Glitazones increase mitochondrial biogenesis and are associated with ~30% risk reduction for PD

GTZ «ever exposure»

P = 0.003, HR 0.72



Cox regression

Glitazone Treatment and Incidence of Parkinson's Disease among People with Diabetes: A Retrospective Cohort Study

Ruth Brauer[1]*, Krishnan Bhaskaran[1], Nishi Chaturvedi[2], David T. Dexter[3], Liam Smeeth[1], Ian Douglas[1]

Movement Disorders RESEARCH ARTICLE

Glitazone Use Associated With Reduced Risk of Parkinson's Disease

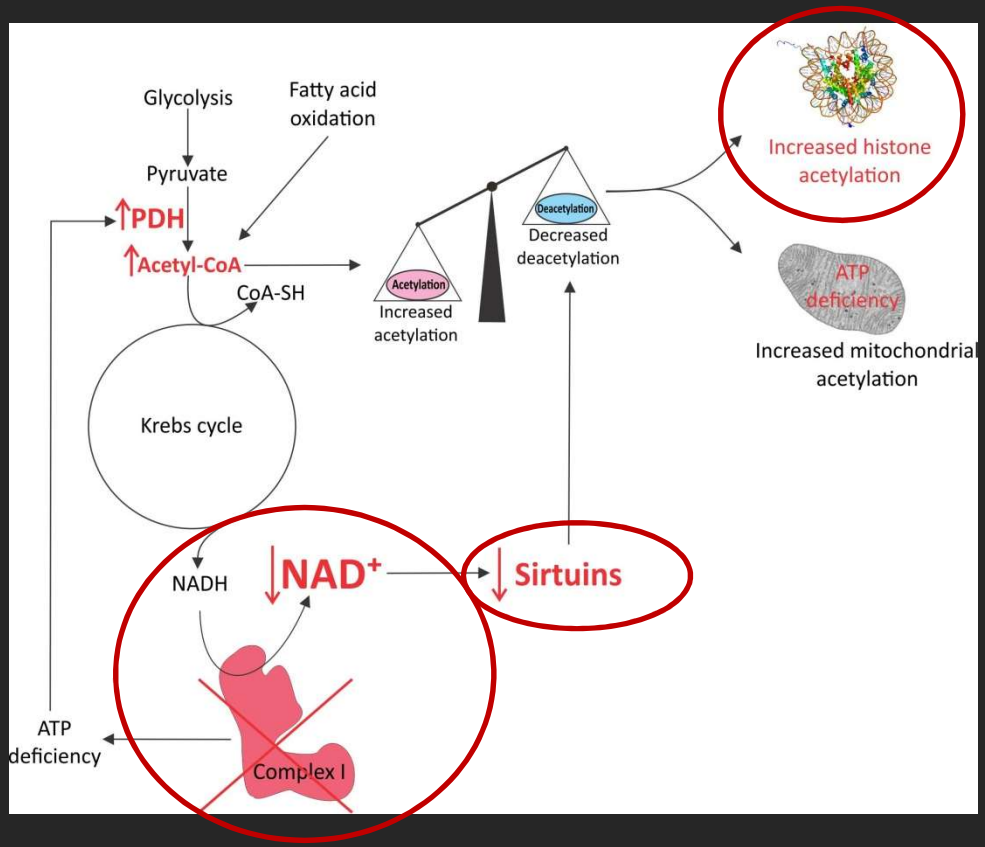
Brage Brakedal, BA, MD,[1,2] Irene Flønes, MD,[1,2] Simone F. Reiter, MD, PhD,[1,2] Øivind Torkildsen, MD, PhD,[1,2] Christian Dölle, PhD,[1,2] Jörg Assmus, PhD,[3] Kristoffer Haugarvoll, MD, PhD [1,2†] and Charalampos Tzoulis, MD, PhD [1,2†*]

Brage Brakedal

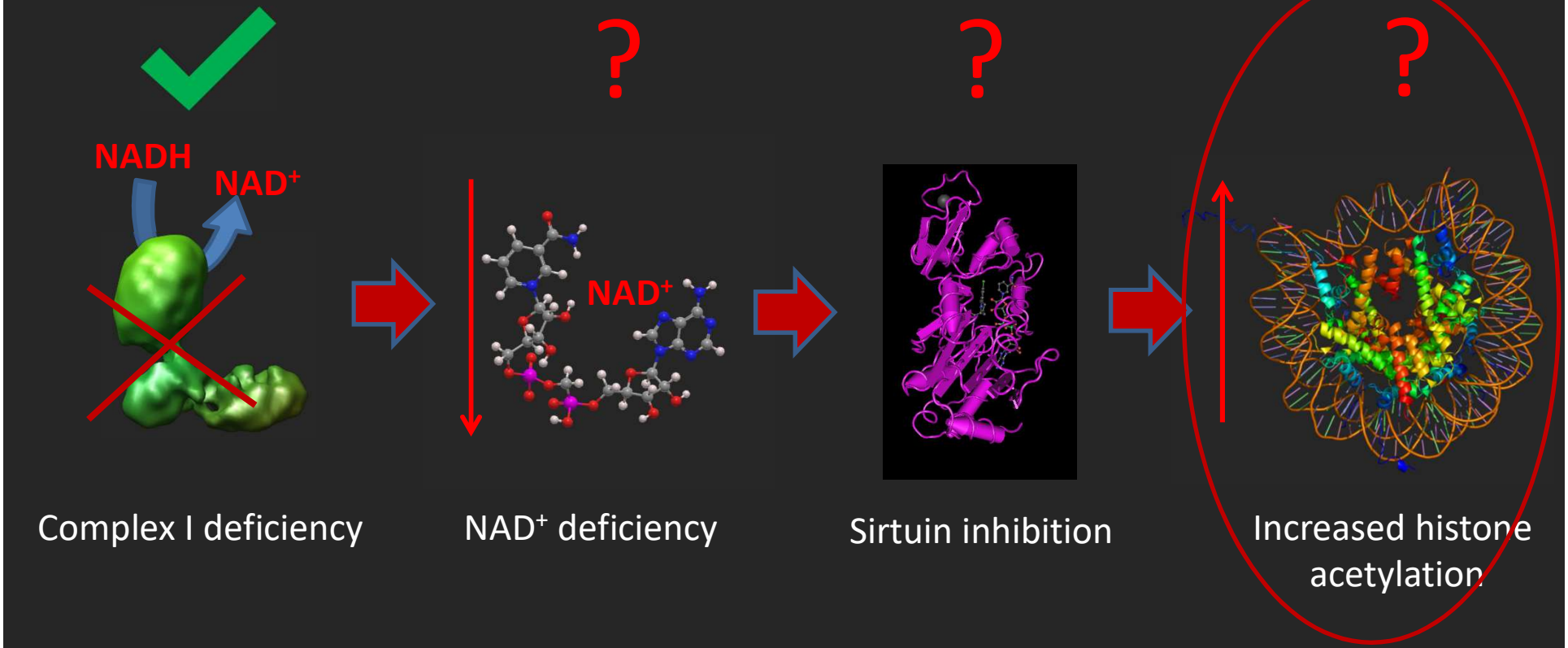
Summary

1. Impaired mitochondrial function plays an important role in the pathogenesis of Parkinson's disease
2. Pharmacological approaches to restore mitochondrial function may have merit as neuroprotective therapies for Parkinson's disease

Complex I deficiency causes NAD+ depletion and histone hyperacetylation

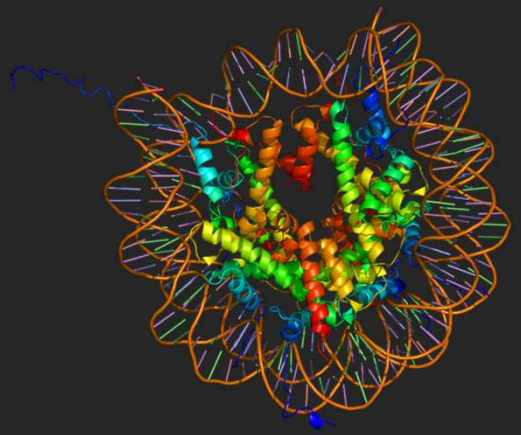


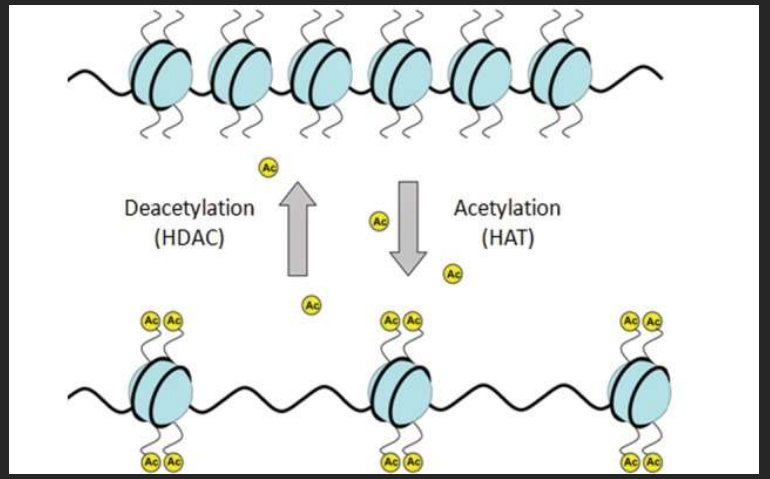
Is there NAD^+ deficiency in PD?



Histone acetylation regulates gene expression

- Increased histone acetylation > increased gene expression



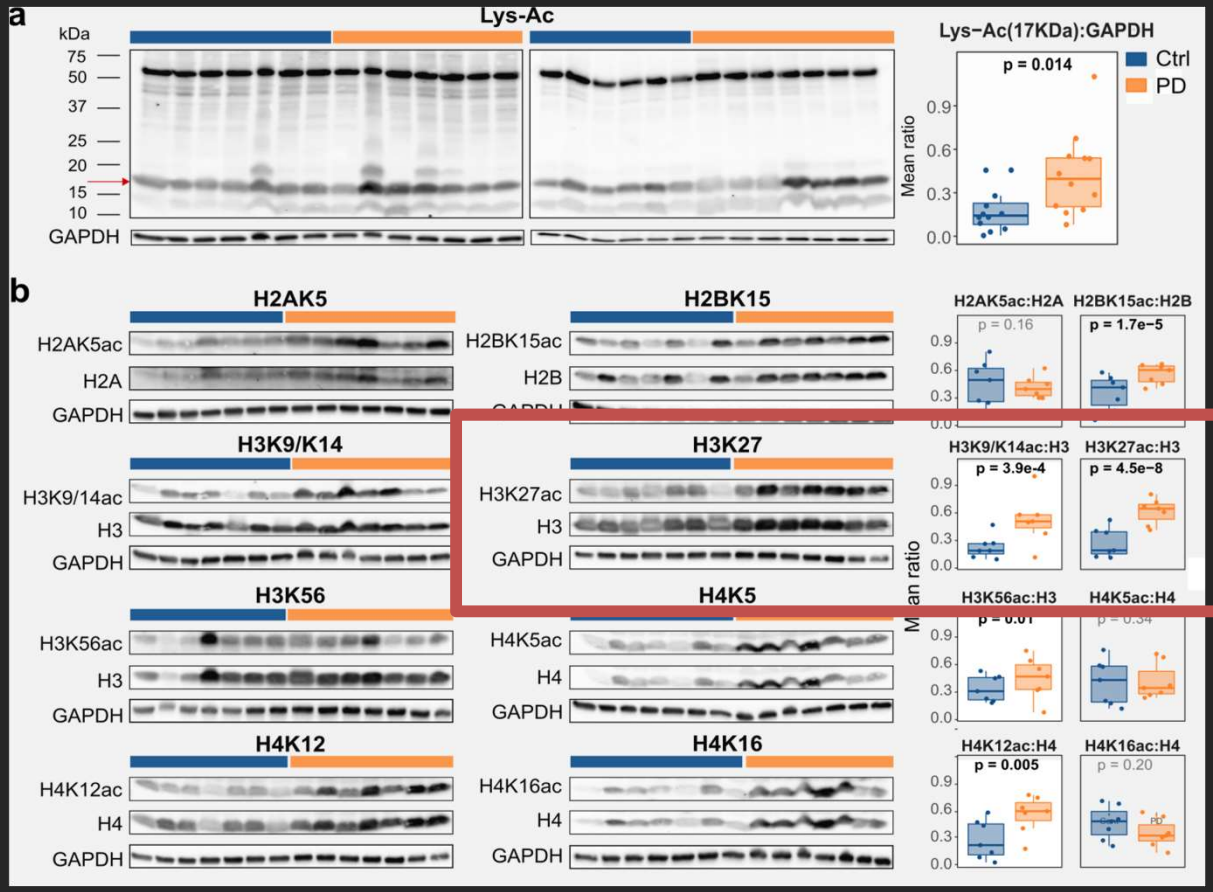


Brain tissue

- Pathology-confirmed PD
  - ParkWest, n = 30
  - Netherlands Brain Bank, n = 21
- Neurologically and neuropathologically healthy controls
  - n = 50

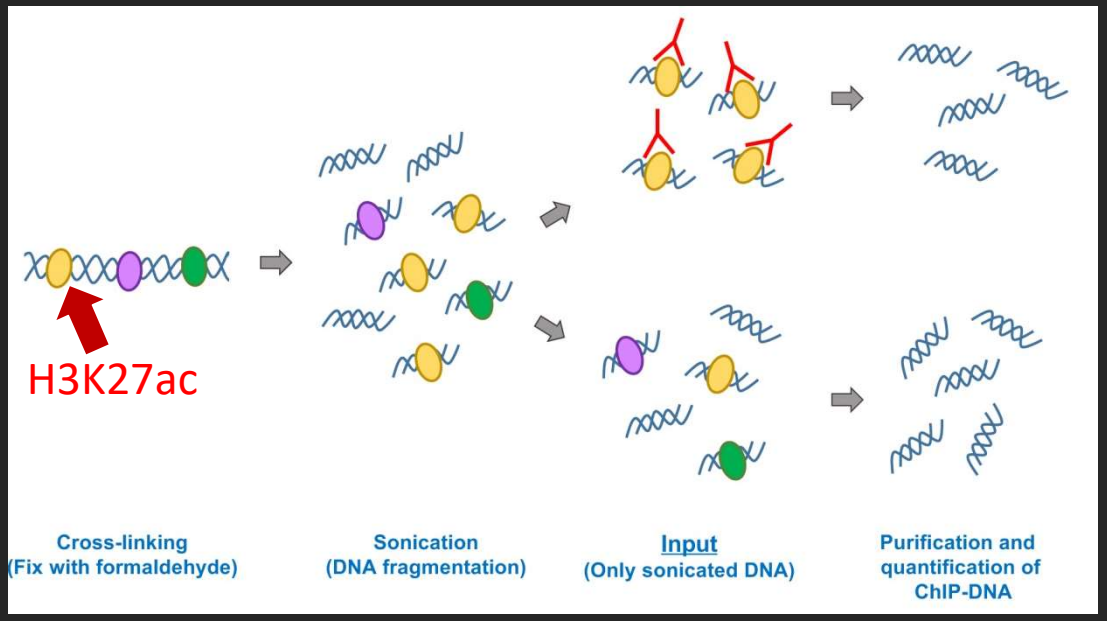
Prefrontal cortex
Brodmann 9-10

Histone hyperacetylation in PD

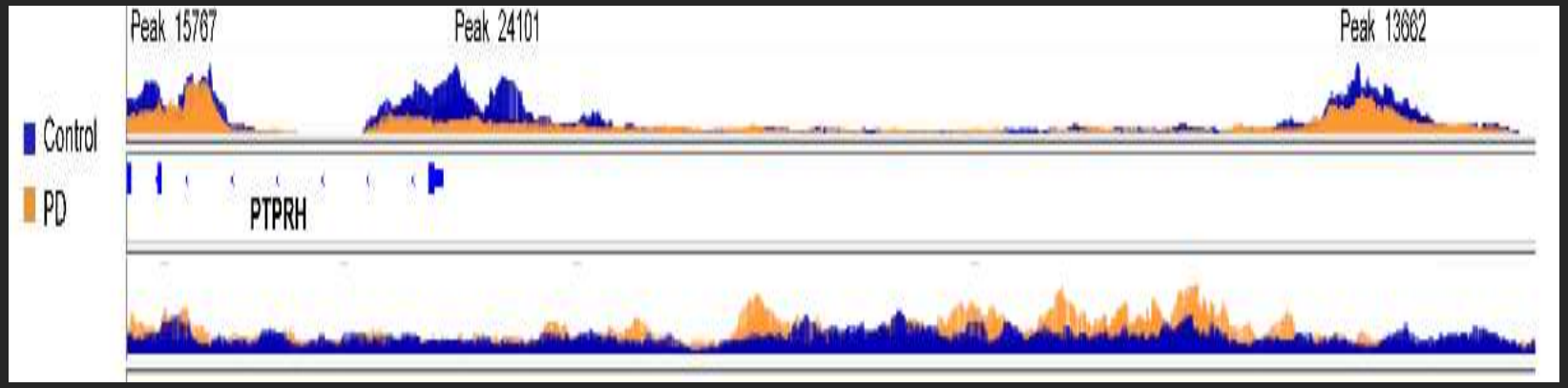


Genome-wide mapping of H3K27ac

- Chromatin Immunoprecipitation Sequencing (ChIP-Seq)



First insight into the genomic landscape of histone acetylation in PD



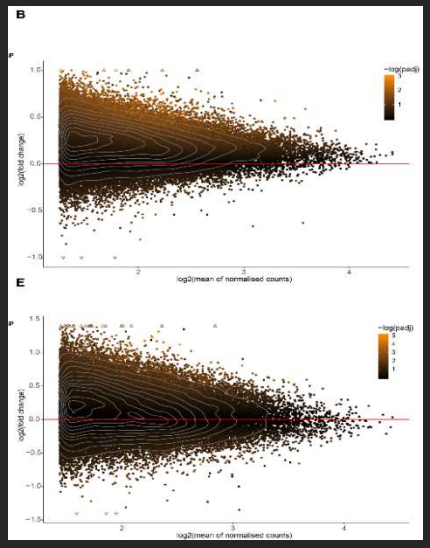
Chromatin Immunoprecipitation Sequencing (ChIP-Seq) for H3K27ac

H3K27 hyperacetylation is a genome-wide phenomenon in PD

H3K27 hyperacetylation

Norwegian

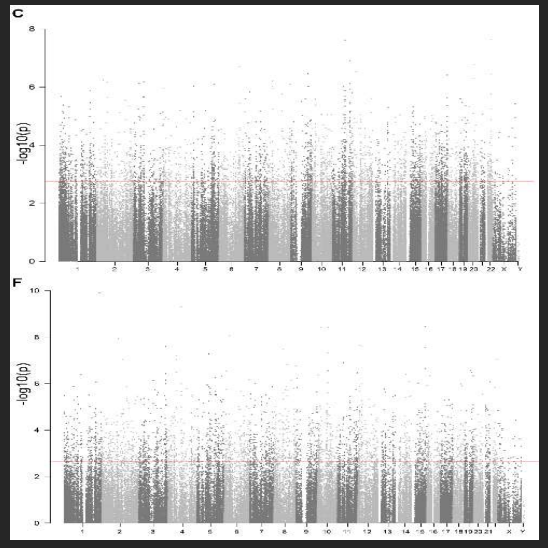
Dutch



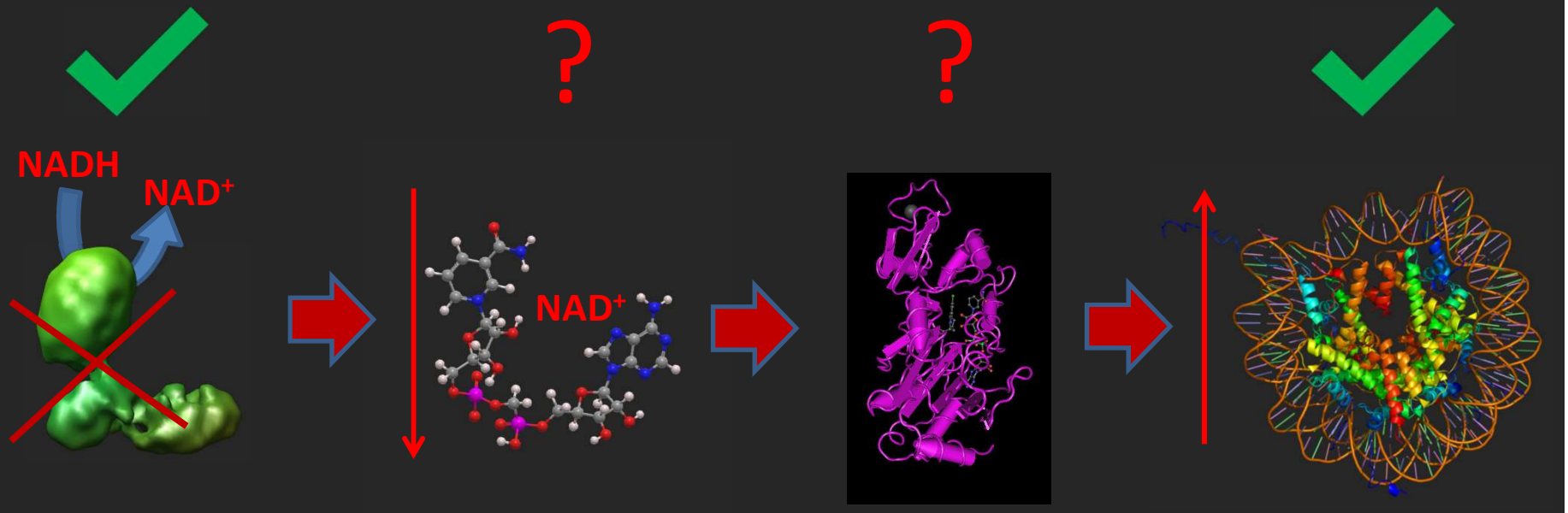
Multiple significant differentially acetylated genes

Norwegian

Dutch



Is there NAD^+ deficiency in PD?



Complex I deficiency

NAD^+ deficiency

Sirtuin inhibition

Increased histone acetylation

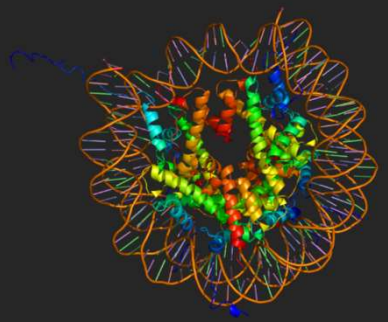
Conclusion

- Genome-wide increase in histone(H3K27) acetylation in Parkinson's disease
- Histone acetylation is severely dysregulated and decoupled from gene expression in Parkinson's disease

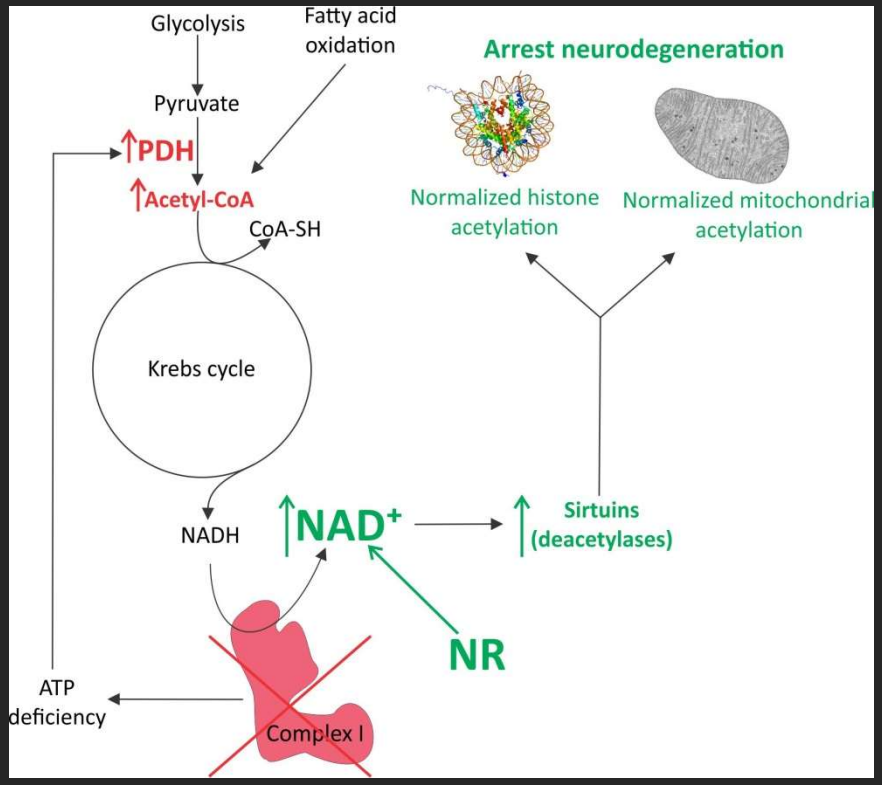

Lilah Toker


Gia Tran


Janani Sundaresan

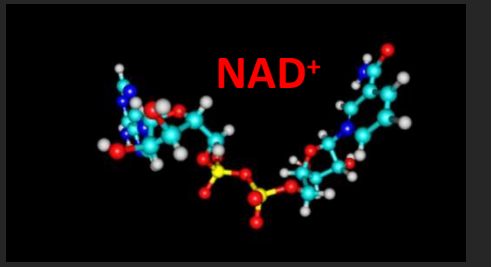


Clinical value: NAD deficiency can be corrected with nicotinamide riboside



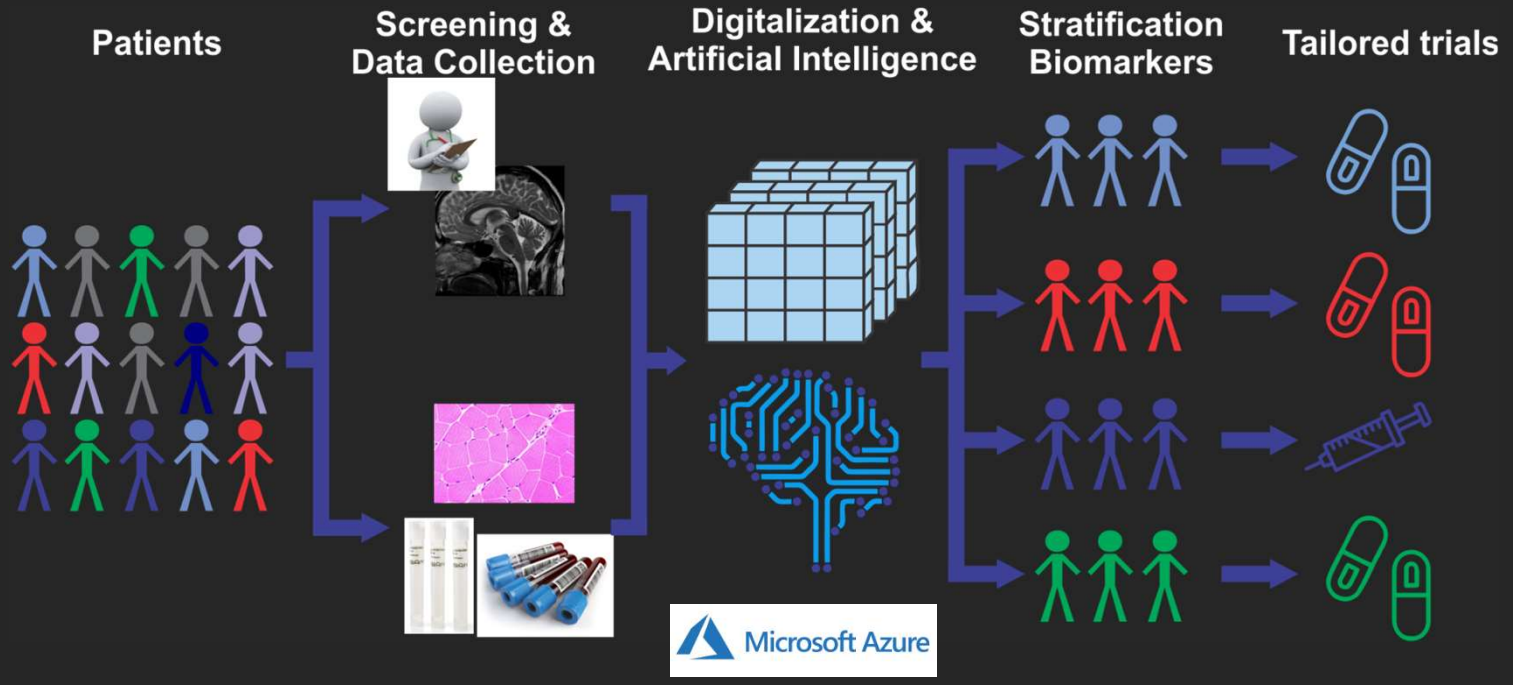
NAD-PARK & NO-PARK: NAD-replenishment therapy in PD

- Nicotinamide Riboside vs. placebo
- NAD-PARK: 01/03/2019
  - n = 30 patients from Bergen
- NO-PARK: 15/03/2020
  - n = 400 patients from 4 RHF



Brage Brakedal

Neuro-SysMed



Neuro-SysMed

Neuro-SysMed

NEUROMICS

Funding:

The Research Council of Norway

HELSE VEST

BERGENS FORSKNINGS STIFTELSE

Collaborators:

UNIVERSITY OF CAMBRIDGE

ICM Brain & Spine Institute

ISTITUTO NEUROLOGICO CARLO BESTA

PARKINSON'S PROGRESSION MARKERS INITIATIVE
Play a Part in Parkinson's Research

PARKWEST

neuromics.org

Neuromics Group

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