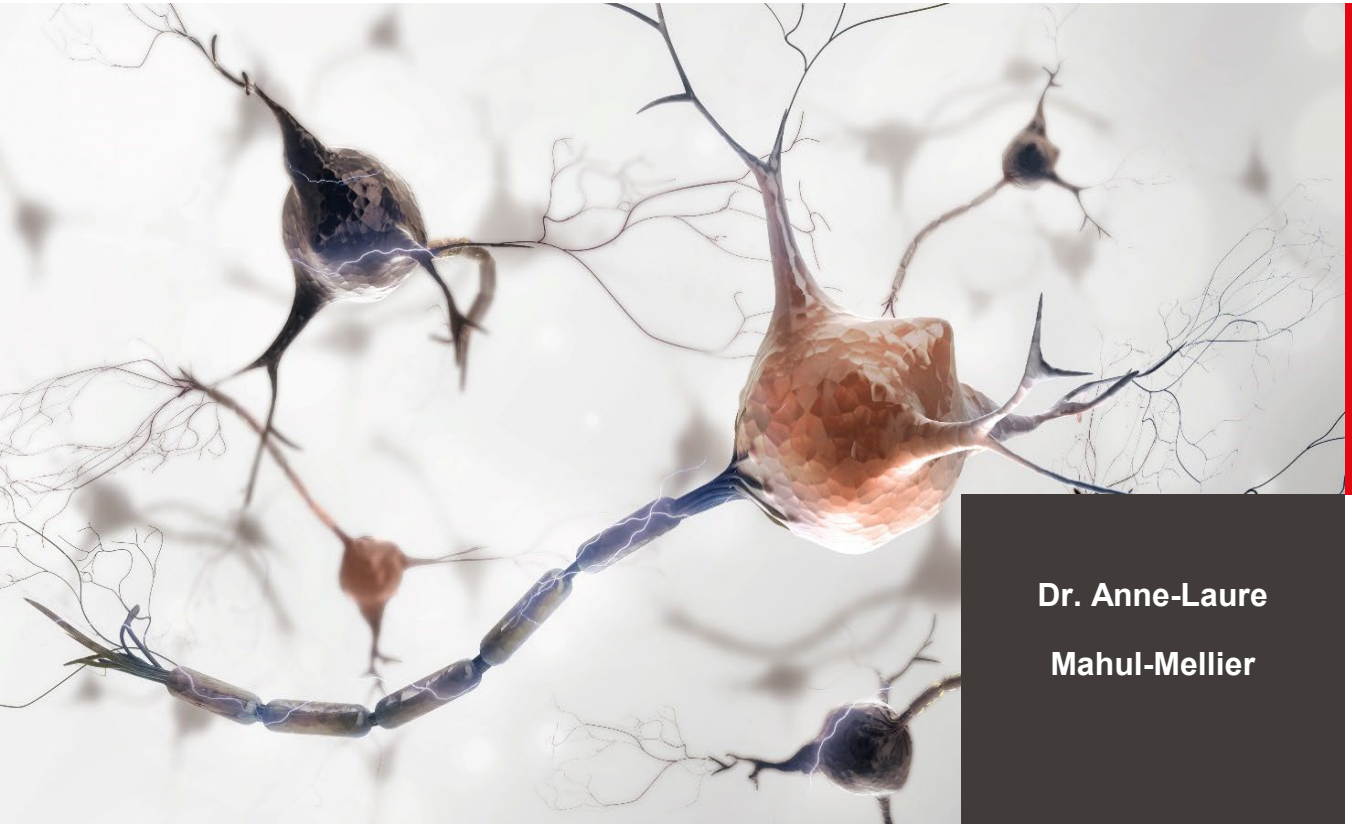
EPFL



Strategic Approaches to PD Therapy

Dr. Anne-Laure Mahul-Mellier

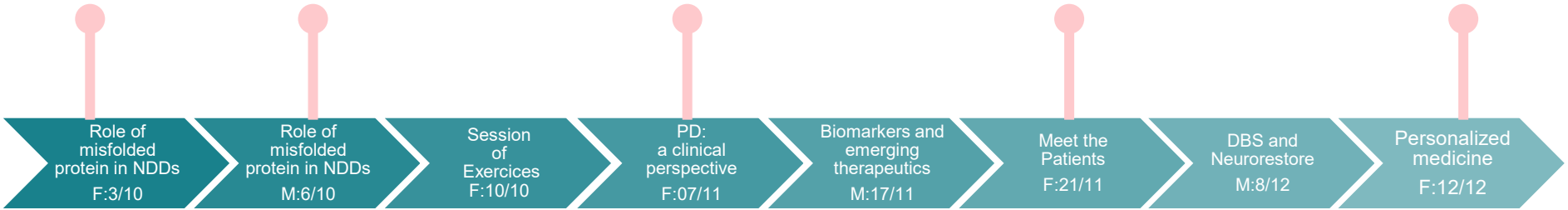
Course organisation:

From proteins misfolding, to aggregation pathways, through spreading in NDDs

Dr. Julien Bally, *Head of the Movement Disorders Unit*

PD patients Session

iPSCs, organoid and AI in advancing therapies



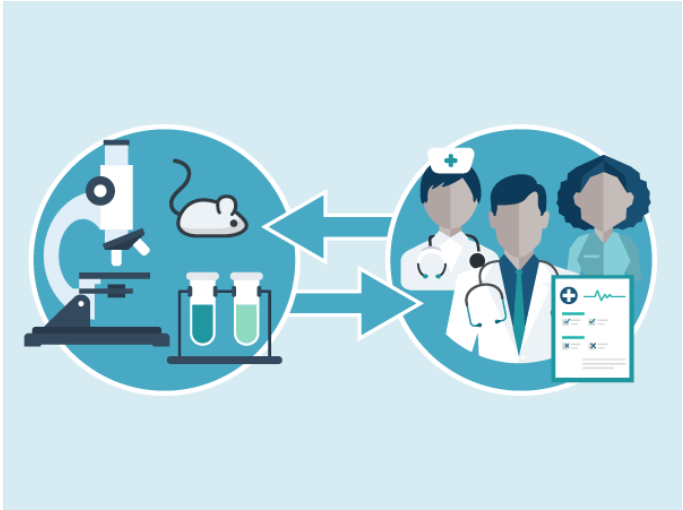
2-hour exercise session With Lukas ☺

Overview of the latest advances in drug design and therapies

Prof. Eduardo Moraud

Understand the biology underlying the pathogenesis of PD: What does it matter?

Implications for Therapeutic Strategies



Brainstorming Challenge:
Where would *you* intervene in PD Pathology?

Case:

You have an **unlimited budget and technology**.
➔Design **one** therapeutic strategy for synucleinopathies (PD, DLB, MSA, etc.) that can prevent/slow down/prevent the disease.

Specify:

•Your **target** (what exactly are you attacking or rescuing?)
Explain your biological assumptions that your strategy is relying on
•The **type of therapy** (drug, antibody, gene therapy, cell therapy, device…).
•At which **stage of the disease would the treatment be given**?
•How do you define your patient cohort?
•How do you **measure your success**?
•Finally, write down **the biological assumptions** your strategy is relying on.

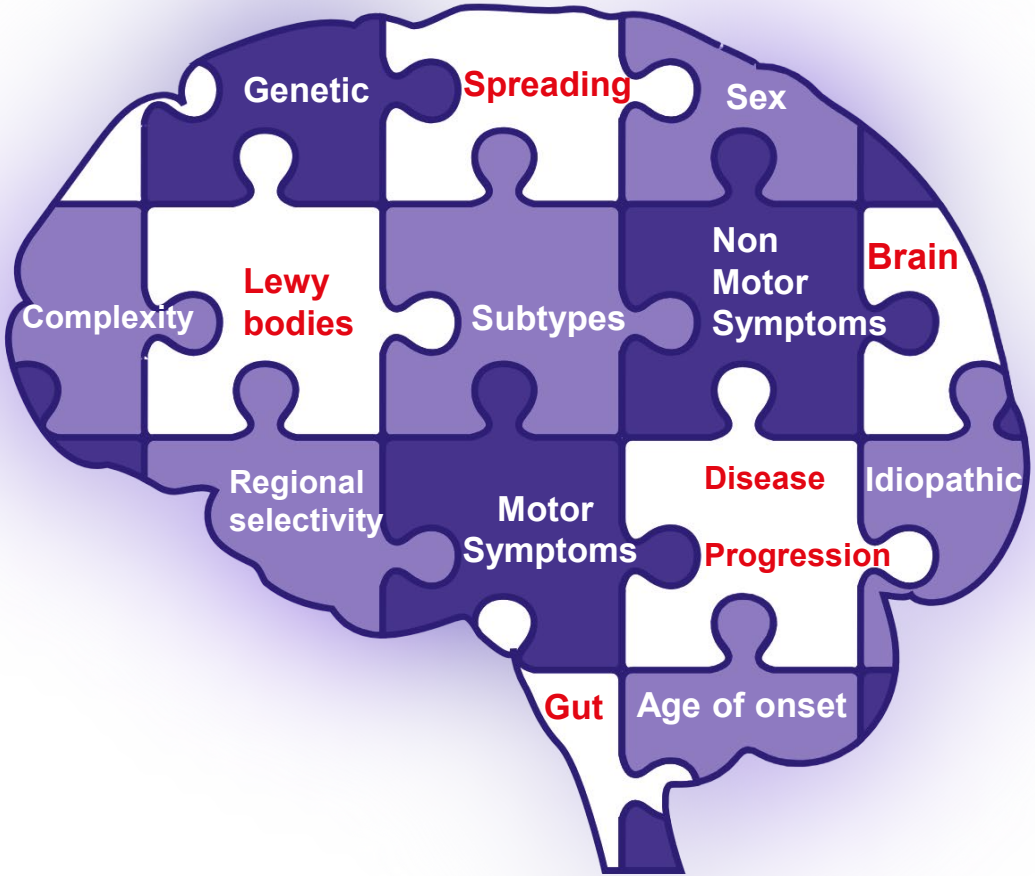
Brainstorming Challenge:
Where would *you* intervene in PD Pathology?

Strategy category	Implicit assumption	Key unknowns / problems
Target Lewy bodies (LBs)		
Lower total aSyn (e.g., gene silencing)		
Replace endogenous aSyn		
Prevent propagation / seeding		
Boost degradation (autophagy/proteasome)		
Downstream neuroprotection (mitochondria, inflammation, oxidative stress, iron deposition…)		

Brainstorming Challenge:
Where would *you* intervene in PD Pathology? ★

Strategy category	Implicit assumption	Key unknowns / problems
Target Lewy bodies (LBs)	LBs are the toxic species	Are LBs cause or consequence? Protective or toxic? What about intermediate species such as soluble oligomers?
Lower total aSyn (e.g., gene silencing)	aSyn is mostly harmful in PD patients who have developed the disease	aSyn is involved in synaptic vesicle trafficking; how much can we safely reduce it in the long term? Compensatory mechanisms?
Replace endogenous aSyn	Recruitment of “normal” aSyn to the aggregates ➔Loss of normal aSyn function contributes to pathology	Risk of promoting aggregation if overexpressed.
Prevent propagation / seeding	Cell-to-cell spread is central driver	In humans, how much progression is due to spread vs local vulnerability? Are we targeting the right species (oligomers vs fibrils)?
Boost degradation (autophagy/proteasome)	Simply “more clearance” = less toxicity	Which form is cleared by which pathway? Could we also degrade essential proteins and cause other toxicity?
Downstream neuroprotection (mitochondria, inflammation, oxidative stress, iron deposition…)	aSyn is “upstream,” downstream is safer to target	How specific are these changes to α-syn vs general aging? Will we actually modify the core disease, or only symptoms?

Mapping the landscape of heterogeneity in Parkinson's Disease :
From patients to the cellular pathology of Lewy Bodies



Parkinson's Disease :
In numbers

Prevalence:
10 millions
patients
2024

worldwide

~25 millions
2050
+112%

60% increase in the number of cases over 20 years
20'000 euros/patient/year

Cost:
€250
billions
annual

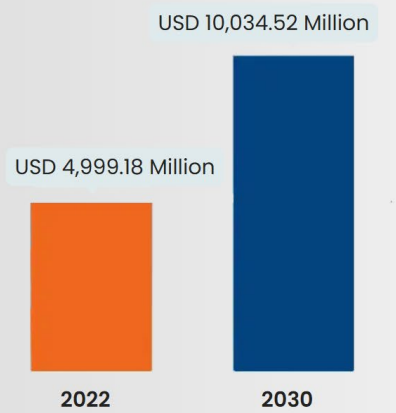
Parkinson’s Disease in numbers

Pharma point of view

Global Parkinsons Disease Treatment Market

Market Size in USD Billion

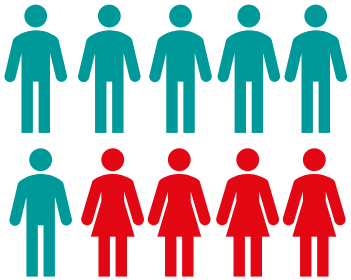
CAGR : 9.10%



Forecast Period	2023 –2030
Market Size (Base Year)	USD 4,999.18 Million
Market Size (Forecast Year)	USD 10,034.52 Million
CAGR	9.10 %
Major Markets Players	• GlaxoSmithKline plc. • Teva Pharmaceutical Industries Ltd. • Boehringer Ingelheim International GmbH. • Impax Laboratories LLC • AbbVie Inc.

Mapping the landscape of heterogeneity in Parkinson's Disease

From patients to the cellular pathology of Lewy Bodies ★



60% men

40% women

5-10 %
< 50 years old

85-90%
> 60 years old

10-15%
Genetic cases

85-90%
Sporadic cases

Parkinson's Disease:
begins years before motor symptoms appear★

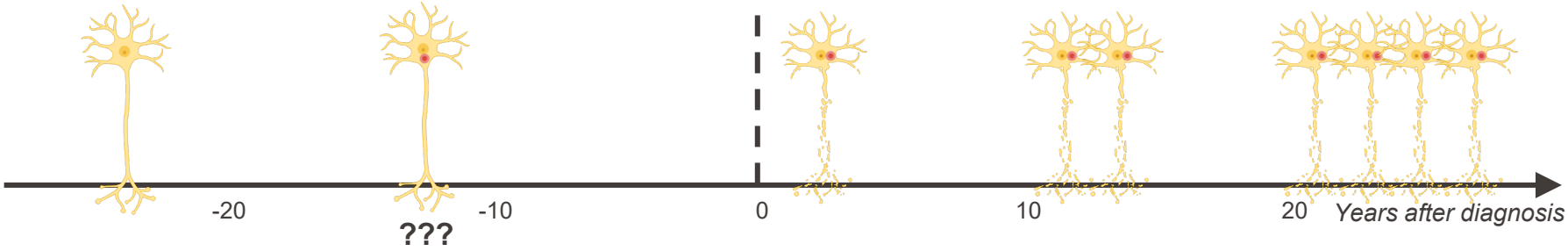
Diagnosis
~58 years old

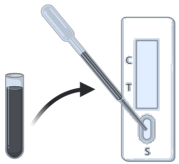
Non-motor symptoms
Constipation, Depression, Sleep disorders, Loss of smell

- No loss of Dopmainergic neurons (yet)
- Pathology starts to form
- And to propagate

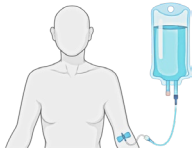
Motor symptoms
Bradykinesia, rigidity, tremor...

- Loss of Dopaminergic neurons > 50%
- Accumulation of the pathology
- Pathology propagate throughout the brain





No biomarker
No test for early diagnosis

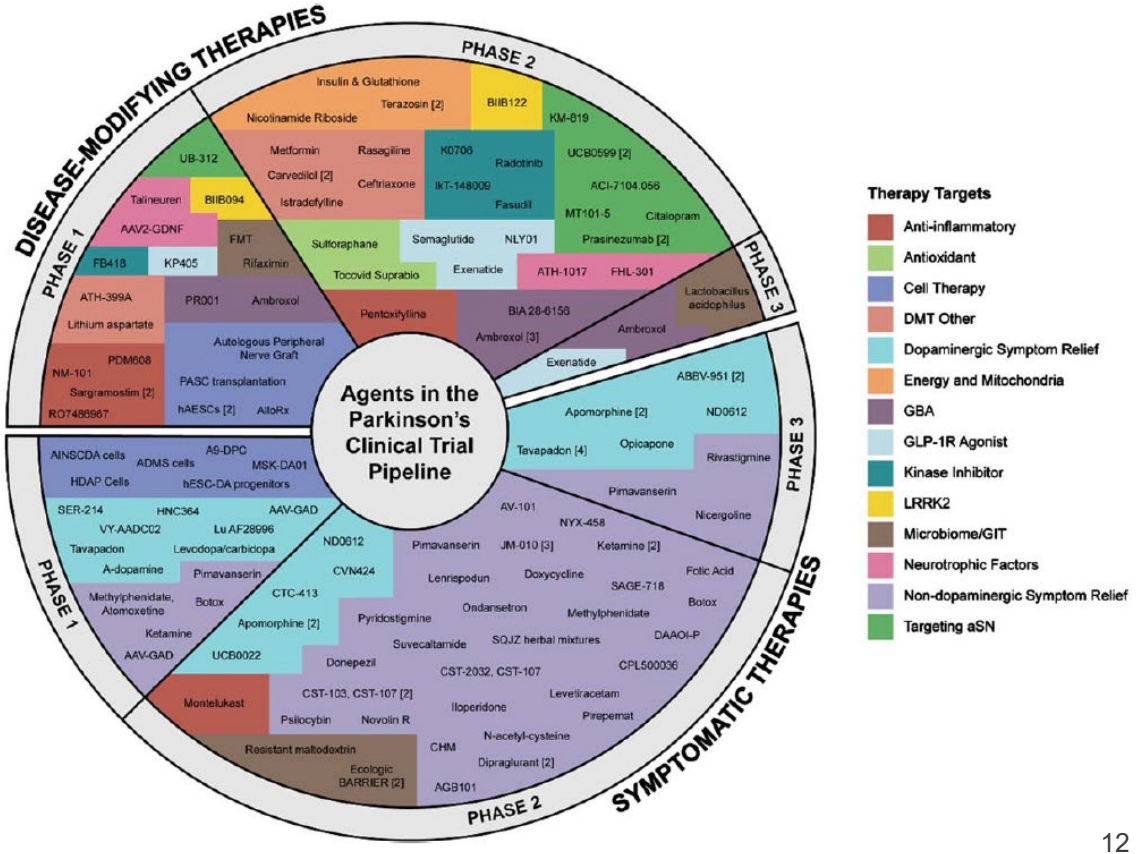


No disease modifying therapies to prevent, slow down or halt PD

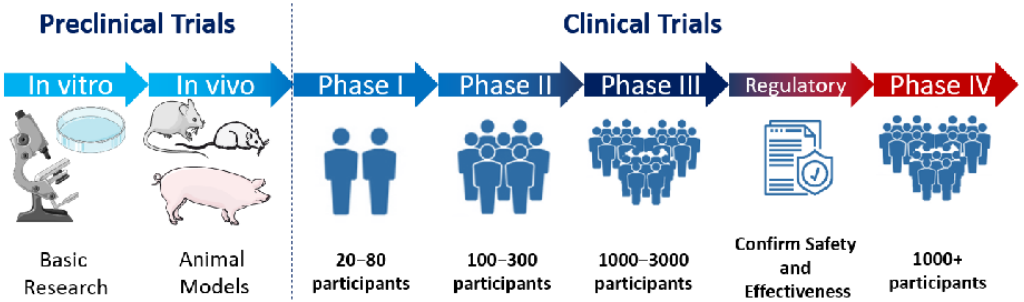
Drug therapies against PD and associated disorders:
On going clinical trials

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

Kevin McFarthing[a], Sue Buff[b], Gary Rafaloff[c], Kenneth Pitzer[d], Brian Fiske[e], Anaya Navangul[f], Katelyn Beissert[f], Aleksandra Pilcicka[f], Rosie Fuest[f], Richard K. Wyse[f] and Simon R.W. Stott[f,*]



Drug therapies against PD and associated disorders: ★
From preclinical research to clinical trials



Stage	Participants	Main Goals	Key Questions
Preclinical	No humans (cells, animals)	Protective mechanisms, toxicity of the drug to the cells or animals	*Is it biologically promising and safe enough to test in humans?*
Phase I	**Mostly healthy volunteers** (sometimes patients if risk too high) ~20–80	Safety, tolerability, pharmacology (drug efficacity➔ body, drug elimination…)	*Is it safe in humans? At what dose?*
Phase II	**Patients only** ~100–300	First efficacy, dose refinement	*Does it show signs of working? What dose is optimal?*
Phase III	**Large patient populations** 300–3,000+	Confirm efficacy & safety	*Is it effective and safe in large populations? Should it be approved?*
Phase IV (optional)	Patients in real-world settings	Long-term monitoring	*How does it perform in real-world conditions?*

Drug therapies against PD and associated disorders:
From preclinical research to clinical trials

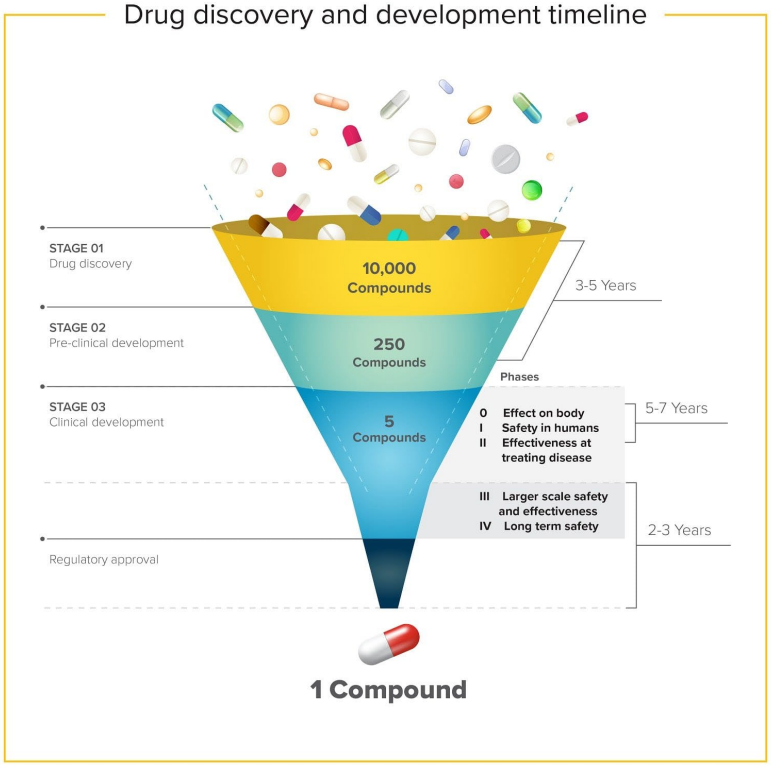


Image source: www.yourgenome.org

- The cost of developing a **new drug** that gets approval is estimated at around **$2-3 billion**.
- Trials which **failed** at phase I or II wasted around $6 million.
- Trial **failed** at phase III resulted in a loss of approximately $77 million.
- The time it takes for an approved drug to reach the market is **10-12 years**.

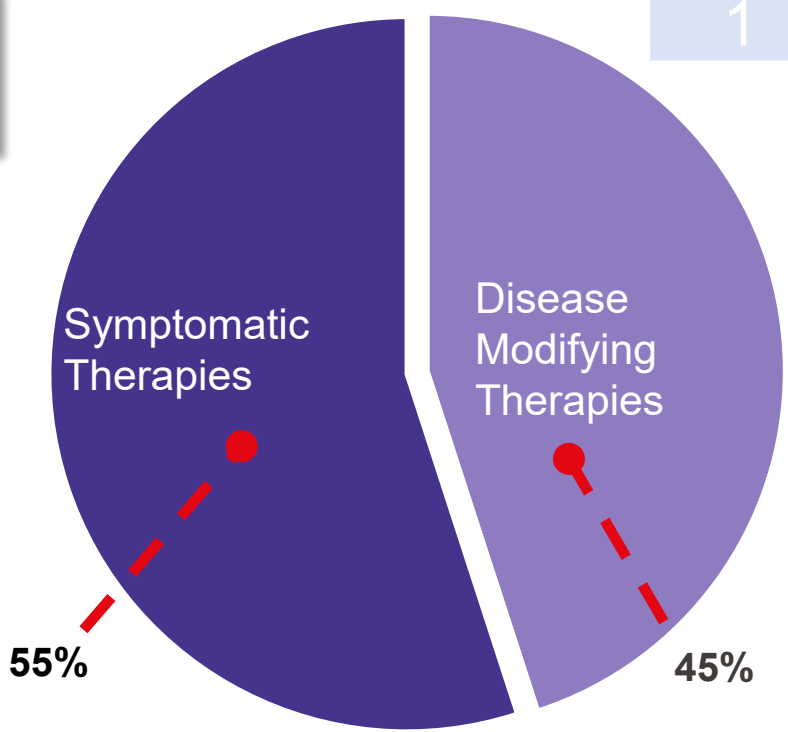
Drug therapies against PD and associated disorders:
On going clinical trials

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

Kevin McFarthing[a], Sue Buff[b], Gary Rafaloff[c], Kenneth Pitzer[d], Brian Fiske[e], Anaya Navangul[f], Katelyn Beissert[f], Aleksandra Pilcicka[f], Rosie Fuest[f], Richard K. Wyse[f] and Simon R.W. Stott[f,*]

139 Clinical trial

17'000 Patients worldwide



Essais cliniques

1 2 3

50% clinical trial are in Phase II =tested on patients

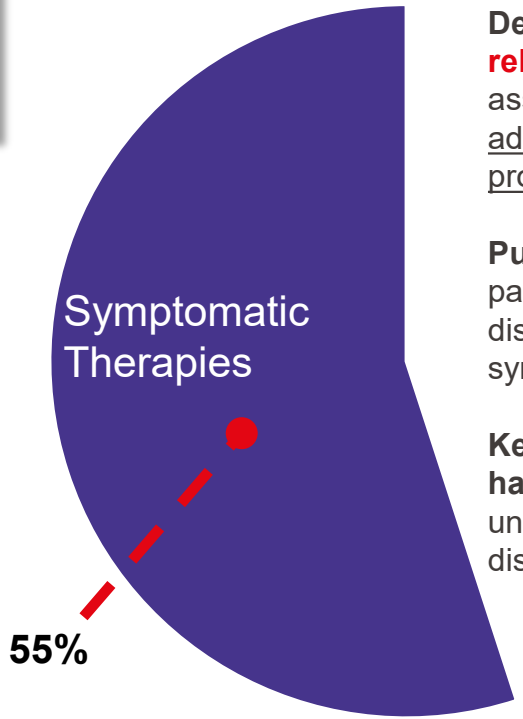
Drug therapies against PD and associated disorders: ★
Symptomatic Therapies

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

Kevin McFarthing[a], Sue Buff[b], Gary Rafaloff[c], Kenneth Pitzer[d], Brian Fiske[e], Anaya Navangul[f], Katelyn Beissert[f], Aleksandra Pilcicka[f], Rosie Fuest[f], Richard K. Wyse[f] and Simon R.W. Stott[f,*]

139 Clinical trial

17'000 Patients worldwide



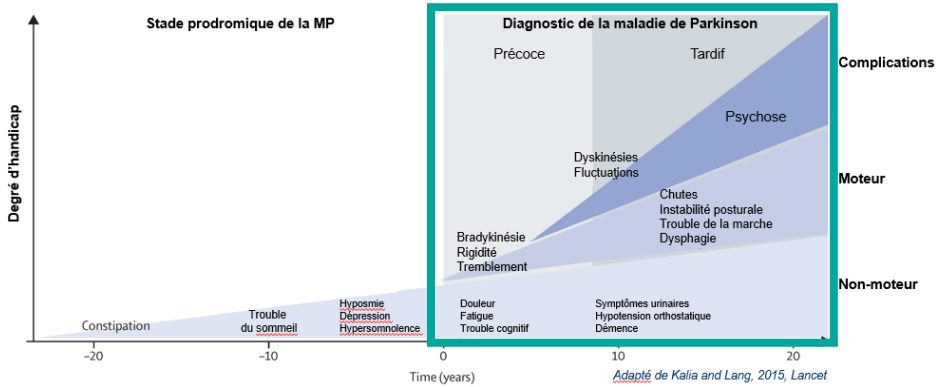
Definition: Symptomatic therapies aim to **relieve or manage the symptoms** associated with a disease without addressing the underlying cause or progression of the disease itself.

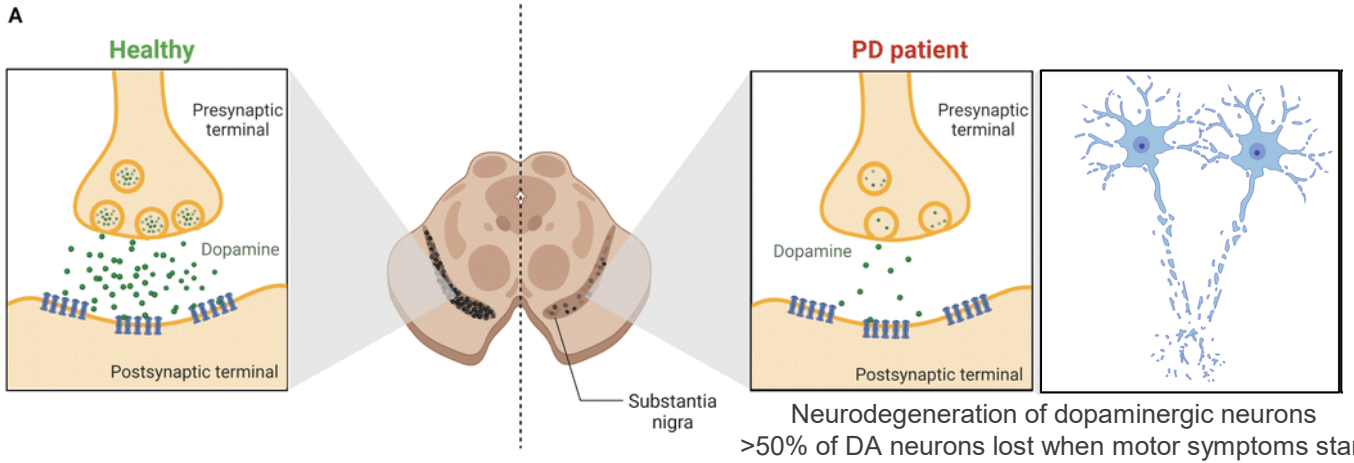
Purpose: These therapies help improve the patient's **quality of life** by reducing discomfort, pain, or other challenging symptoms.

Key Point: Symptomatic therapies **do not halt or slow the progression** of the underlying disease but instead manage the discomfort or limitations it causes.

Current clinical trial in PD ★

Symptomatic therapies *(see lectures Julien Bally and Eduardo Moraud)*



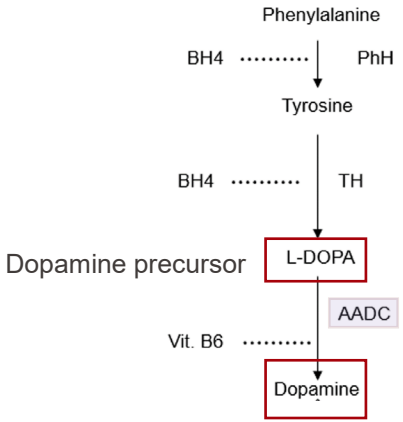


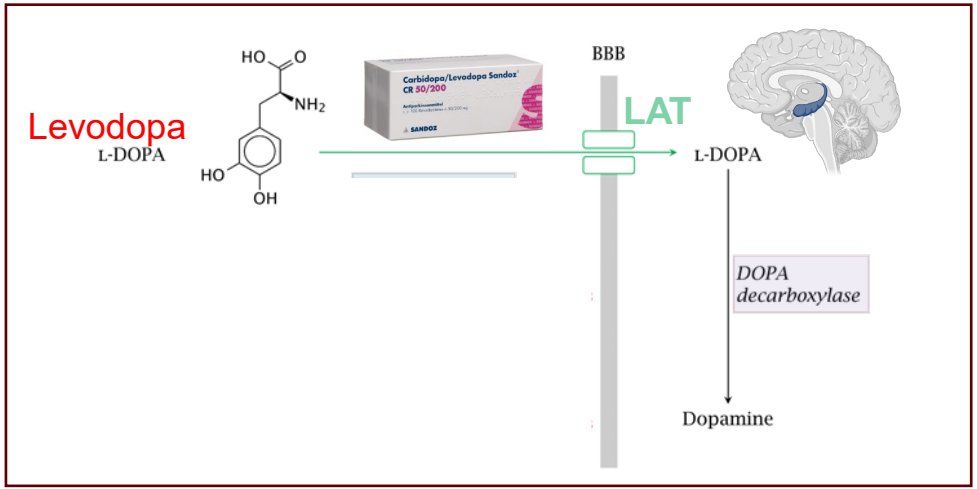
Neurodegeneration of dopaminergic neurons
>50% of DA neurons lost when motor symptoms start

Current clinical trial in PD ★

Symptomatic therapies *(see lectures Julien Bally and Eduardo Moraud)*

Compensate for dopamine deficiency due to neuronal death through medication (Levodopa, dopamine agonists) to reduce the severity of motor symptoms.





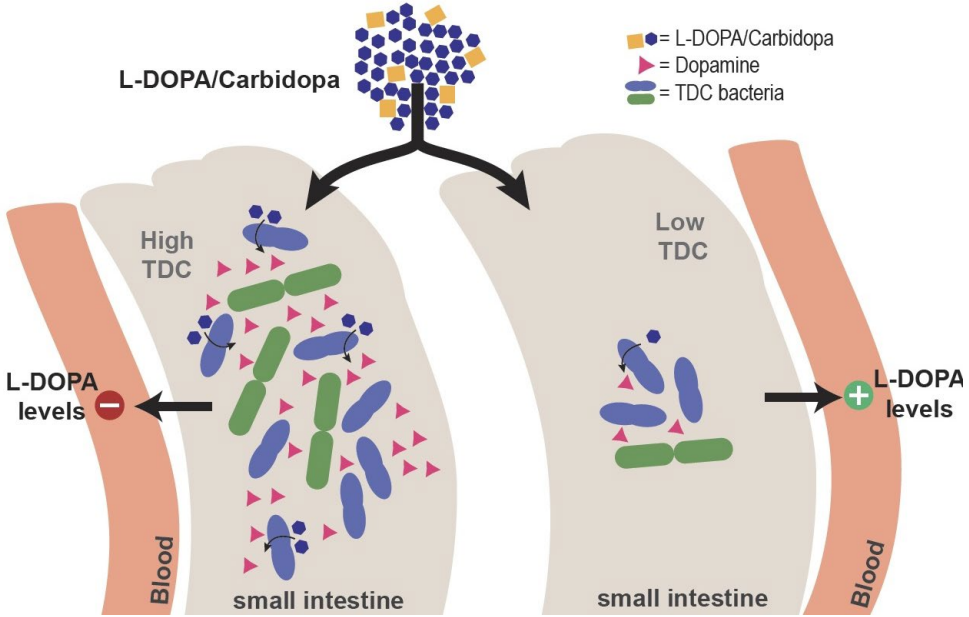
Why Levodopa and not dopamine? Dopamine cannot cross the blood–brain barrier (BBB)
1. BBB endothelial cells have tight junctions that block most molecules.and Dopamine is too polar to cross the lipid membrane.
2. There is no dopamine transporter on the BBB ➔ **Giving dopamine does not increase brain dopamine levels.**

Why does Levodopa work? It crosses the BBB through the Large Amino Acid Transporter (LAT).
Once inside the brain, it is converted into dopamine by **AADC (Aromatic L-Amino Acid Decarboxylase)** ➔ **Levodopa restores brain dopamine.**

Why Carbidopa Is Essential? Carbidopa **inhibits AADC** (Aromatic L-Amino Acid Decarboxylase=DOPA decarboxylase) **outside the brain**, preventing this early conversion. Carbidopa does **not** cross the BBB, so it does not block dopamine formation in the brain.
Benefits of adding Carbidopa: More levodopa reaches the brain + Lower levodopa doses are needed

Origin of the prion-like diseases – case of the PD ★

7. Gut bacteria affect the bioavailability of PD medications such as Levodopa



Certain gut bacteria, particularly *Enterococcus faecalis*, produce an enzyme (tyrosine decarboxylase, **TDC**) that converts levodopa into dopamine in the gut, which cannot cross the blood-brain barrier. This premature conversion **reduces the amount of levodopa that reaches the brain**, potentially making the treatment less effective to control de motor symptoms in PD. **This link microbiota and treatment effectiveness.**

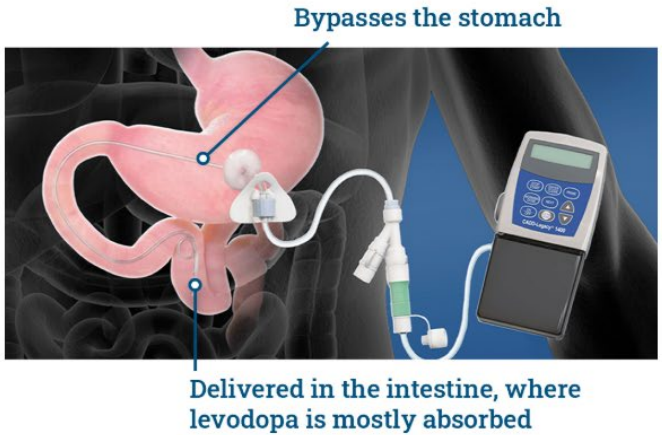
Current clinical trial in PD ★

Symptomatic therapies *(see lectures Julien Bally and Eduardo Moraud)*

Compensate for dopamine deficiency due to neuronal death through medication (Levodopa, dopamine agonists) to reduce the severity of motor symptoms.

BYPASSING THE STOMACH DELIVERS LEVODOPA WHERE YOU NEED IT

Duopa is delivered right into the **intestine**, so your levodopa can be absorbed quickly.



Current clinical trial in PD

Symptomatic/DMT therapies: the DA neurons as a cerebral DOPA pump?

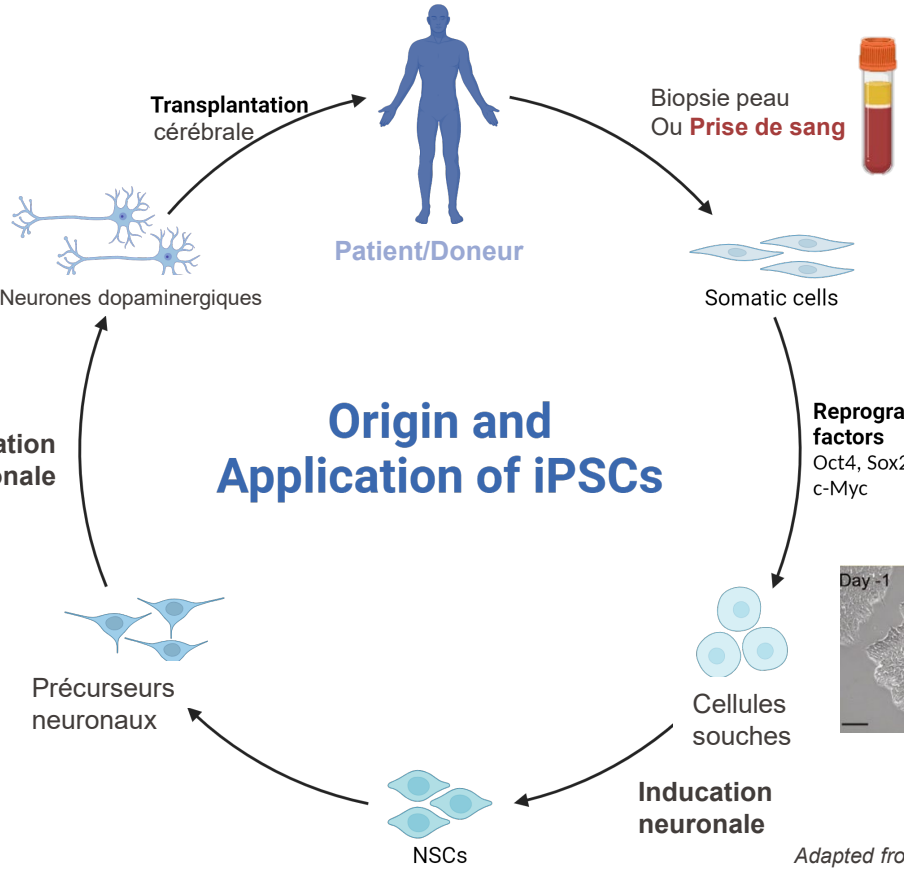
BlueRock THERAPEUTICS | BAYER

Bemdaneprocel (BRT-DA01)
Phase I - 12 patients

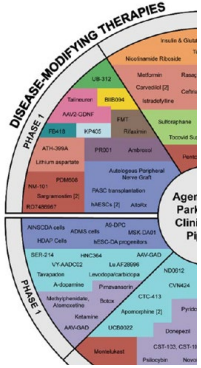
Update on STEM-PD clinical trial – stem cell-based transplant for Parkinson's disease

LUND UNIVERSITY

Phase I - 8 patients



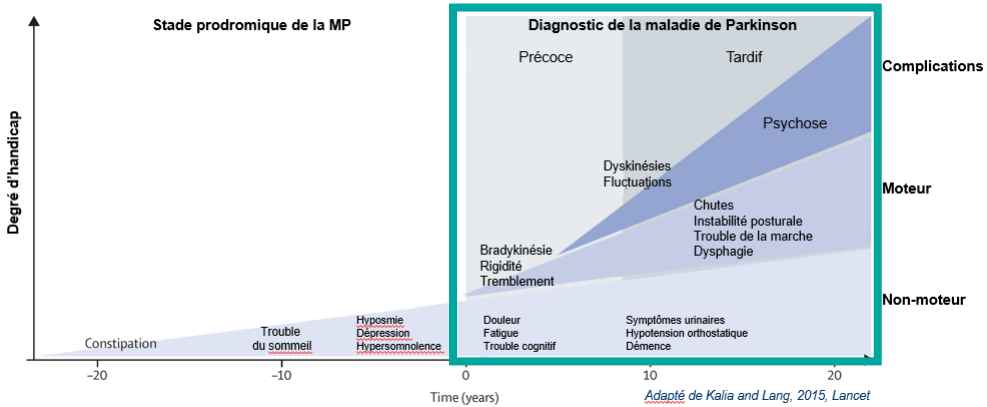
Adapted from Sheta et al., 2023



Cell therapy (8%)

Current clinical trial in PD ★

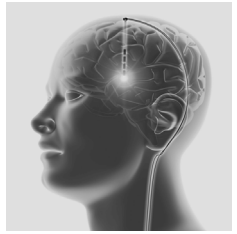
Symptomatic therapies *(see lectures Julien Bally and Eduardo Moraud)*



Adapté de Kalia and Lang, 2015, Lancet

1. Deep Brain Stimulation: Electrical impulses in the thalamus improve neuron communication and reduce motor symptoms (effective in ~10 to 20% of patients).

   ➔ see lecture 8/12/25



Current symptomatic therapies do not prevent neuronal loss, nor do they slow, halt, or prevent disease progression. They primarily improve the daily lives of patients by alleviating motor symptoms.

Current clinical trial in PD ★

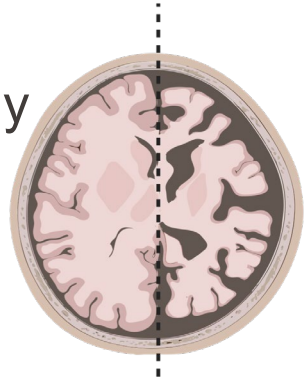
Disease modifying therapies

Definition: Disease-modifying therapies are treatments that aim to impact the underlying mechanisms or causes of a disease to alter its natural progression. **They work to slow, stop, or sometimes even reverse the progression of the disease itself.**

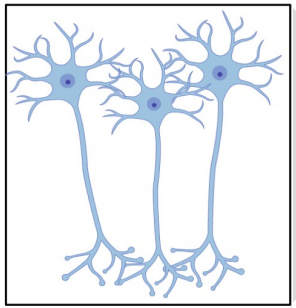
Purpose: These therapies focus on the underlying pathology of a disease, aiming to improve long-term outcomes and potentially change the disease course.

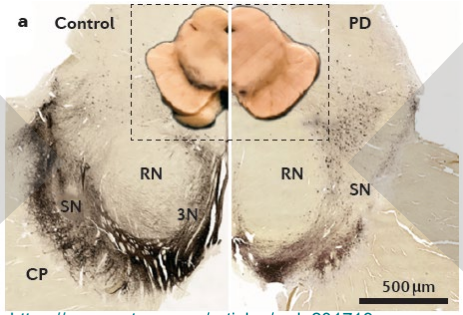
Key Point: Disease-modifying therapies directly affect **the disease's root causes or progression**, aiming for more long-term improvement rather than temporary symptom relief.

Parkinson's Disease:
Main pathological features



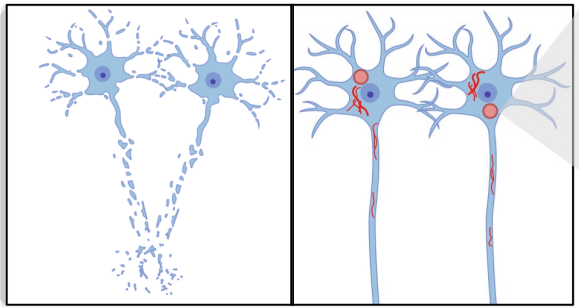
1. Neuronal loss





https://www.nature.com/articles/nrdp201713

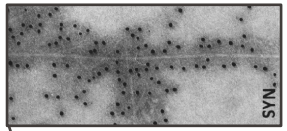
substantia nigra



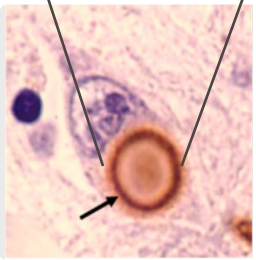
2. Neurodegeneration of dopaminergic neurons

3. Accumulation of inclusions

aSyn fibrils (pathological form)

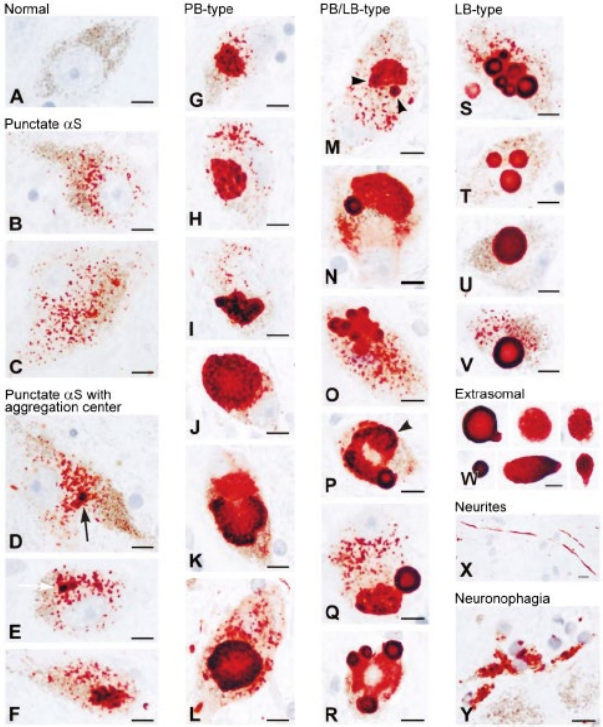


Spillantini et al., 1997

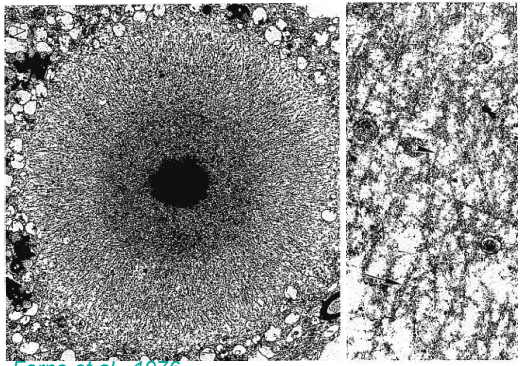


Lewy Body

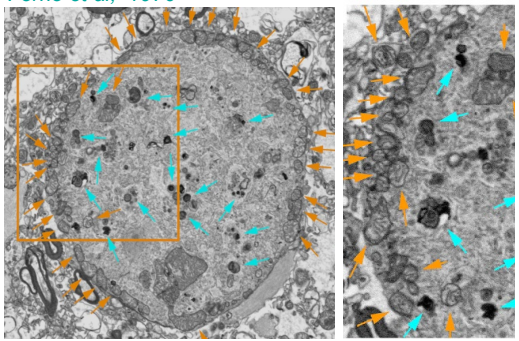
Mapping the landscape of heterogeneity in Parkinson's Disease :
From patients to the cellular pathology of Lewy Bodies



Kuusisto et al, 2003

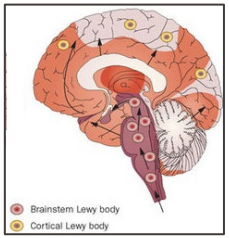


Forno et al, 1976



Shahmoradian and Lewis et al., 2019

Cortical LB

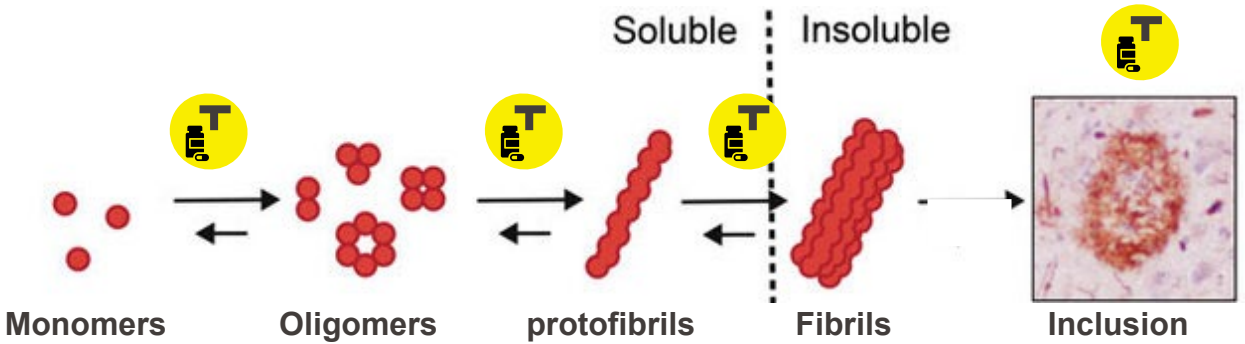


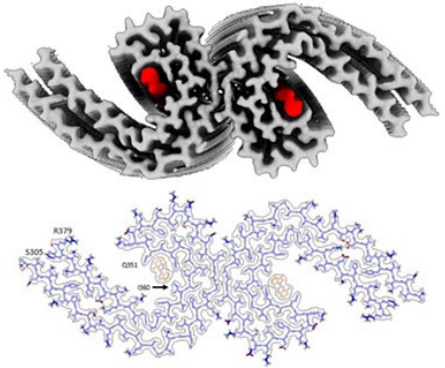
Brainstem LB

Why such heterogeneity? Continuum of morphologies? Co-existing?
Why do different types of neurons form different types of LB?

POV therapeutic strategy: which form shall be targeted?

Mapping the landscape of heterogeneity in Parkinson's Disease : From patients to the cellular pathology of Lewy Bodies ★

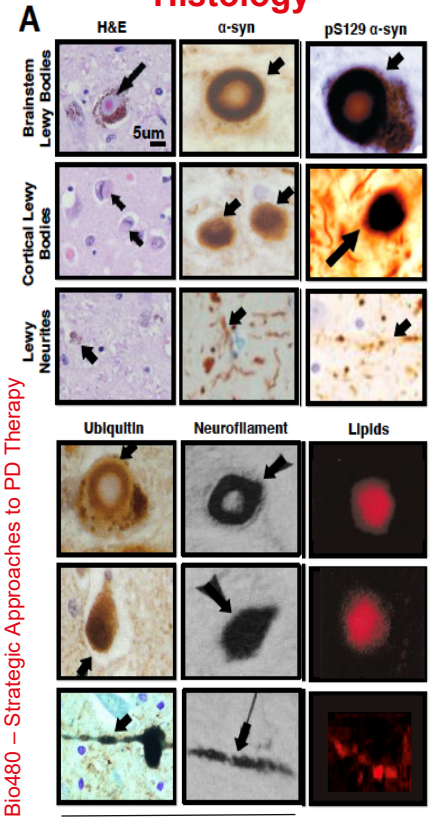




POV therapeutic strategy: which form shall be targeted?

Mapping the landscape of heterogeneity in Parkinson's Disease : From patients to the cellular pathology of Lewy Bodies

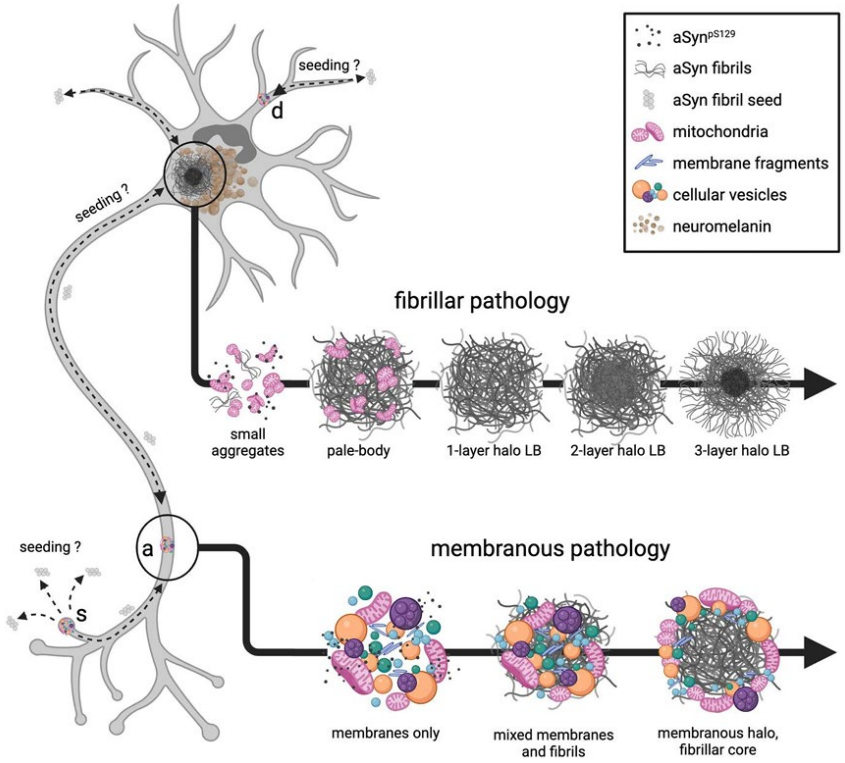
Histology



- > 600 Proteins (proteome)

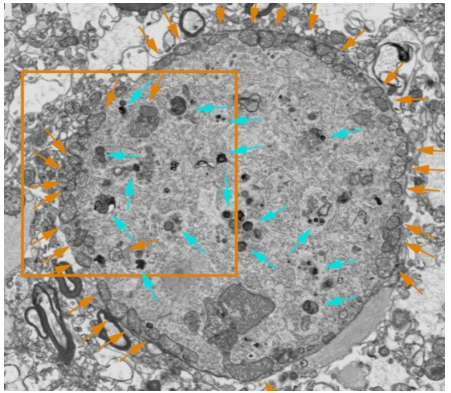
Fares B, and Lashuel HA*, Nat. Rev. Neuroscience, 2021*

What we have learnt so far from human brain tissues



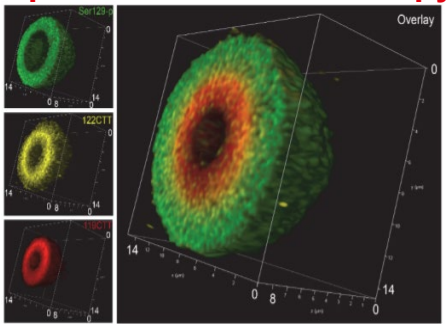
Lewis et al., 2024, BioRXiv

Electron microscopy



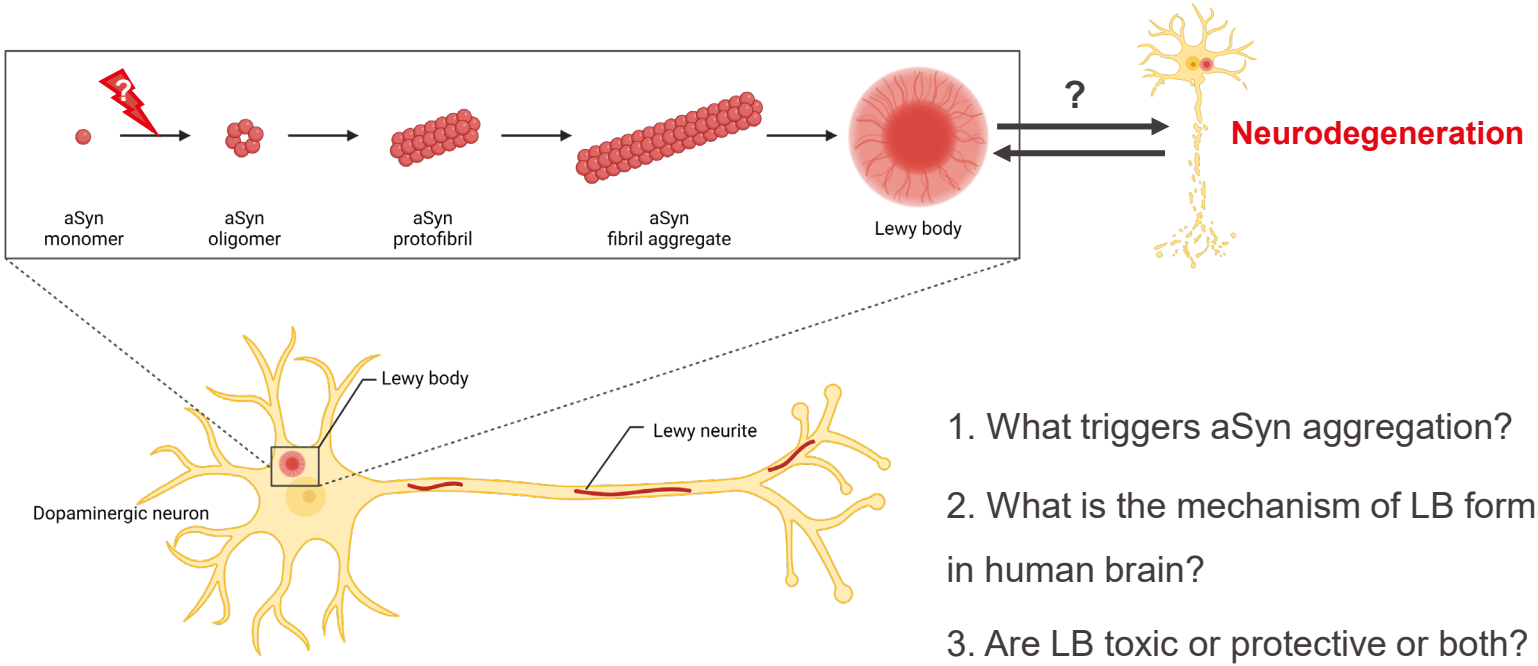
Shahmoradian S et al., Nat. Neuroscience, 2019

Superresolution microscopy



Moors T et al., 2021

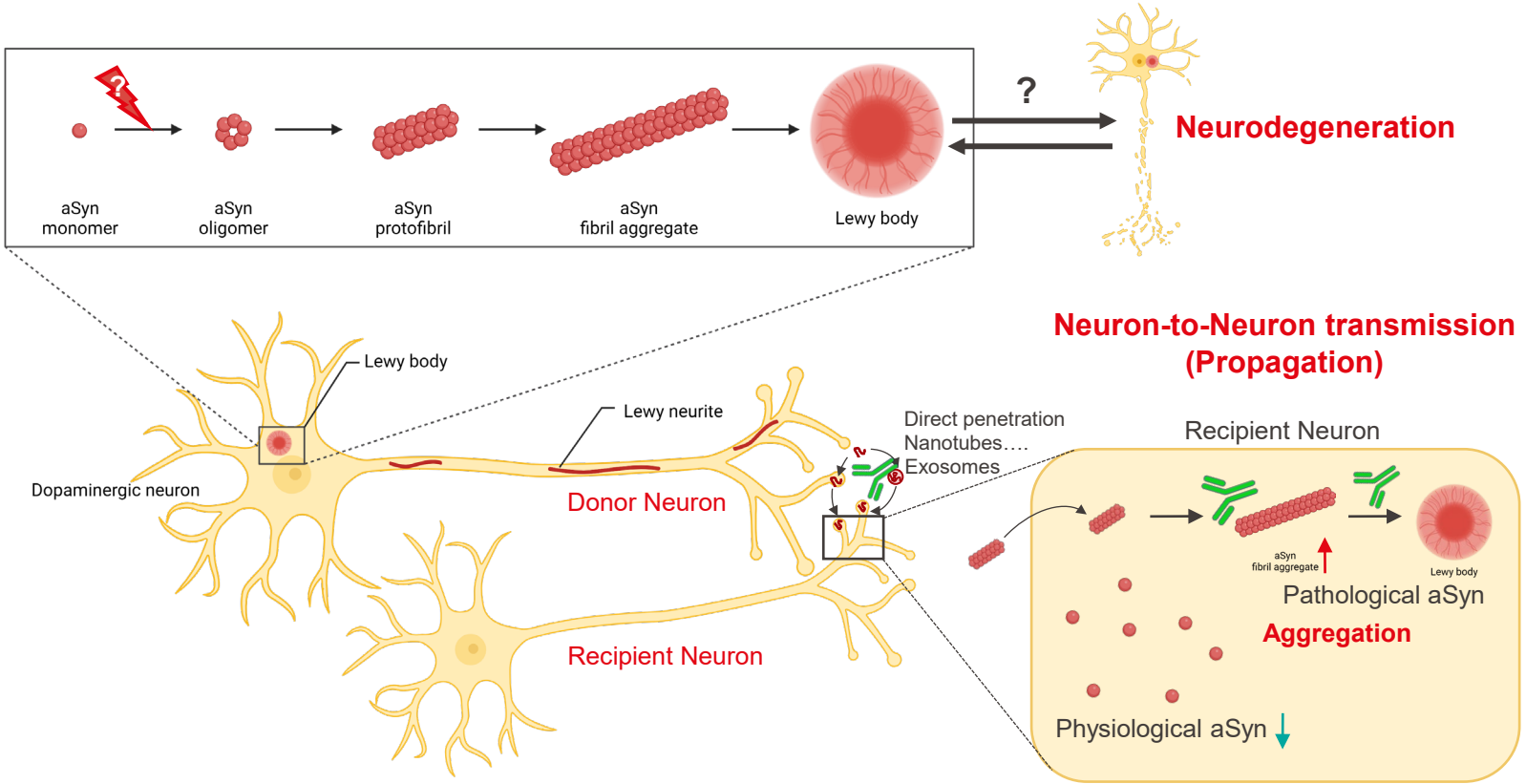
Mapping the landscape of heterogeneity in Parkinson's Disease : From patients to the cellular pathology of Lewy Bodies ★



1. What triggers aSyn aggregation?
2. What is the mechanism of LB formation in human brain?
3. Are LB toxic or protective or both?

Answering these questions is essential for designing relevant therapeutic strategies.

Mapping the landscape of heterogeneity in Parkinson's Disease : From patients to the cellular pathology of Lewy Bodies ★



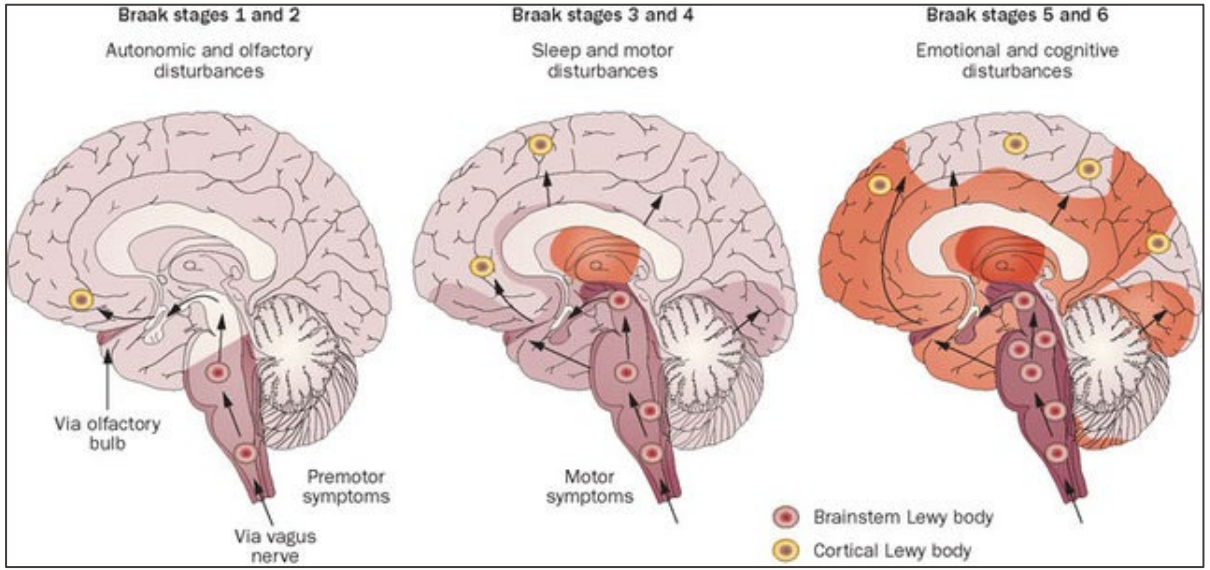
POV Therapeutic strategies: shall we target the physiological aSyn and/ or the pathological aSyn?

Mapping the landscape of heterogeneity in Parkinson's Disease :
From patients to the cellular pathology of Lewy Bodies

small molecules

AC Immune

idorsia



https://www.sciencedirect.com/science/article/pii/S0197458002000659

Immunotherapies

Roche

PASADENA (NCT03100149)

PADOVA
(phase IIb, NCT04777331)
phase IIb,

AC Immune
ACI-7104.056
NCT06015841)

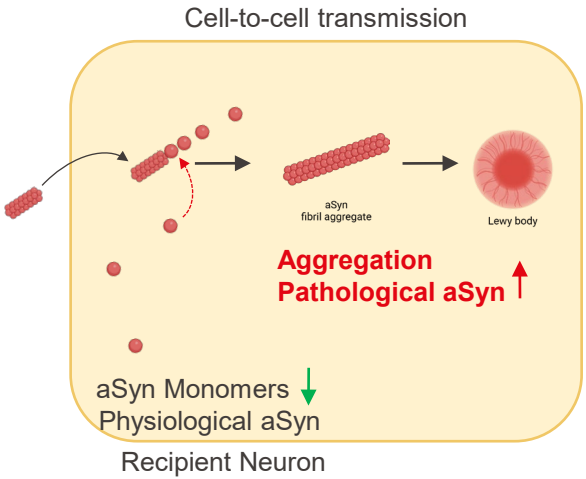
Inspired by patients. Driven by science.

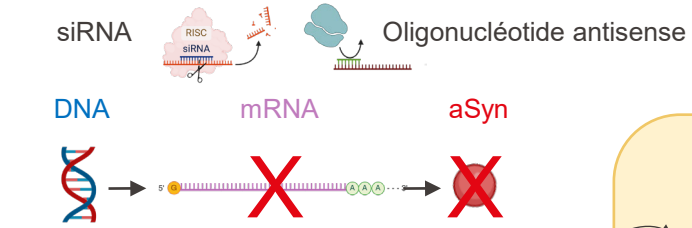
NOVARTIS

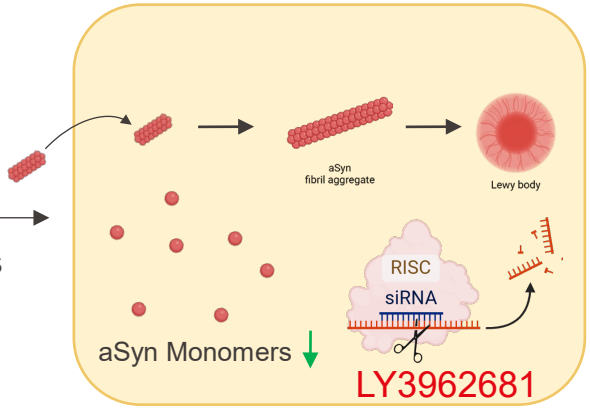
Lundbeck

Phase 3 MASCOT (MSA)

Reduce endogenous alpha-synuclein levels to prevent aggregation ★







ION464
(ANTISENSE oligonucleotide)

CONDITIONS:

Multiple System Atrophy

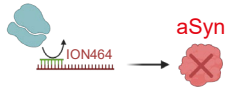
STATUS:

Recruiting

2024

PHASE:

Phase 1



CLINICAL TRIALS ID

NCT04165486

IONIS

First-In-Human Single and Multiple Ascending Dose Trial Design of LY3962681, a Novel Intrathecally Delivered siRNA Targeting α-synuclein mRNA for the Treatment of Patients with Parkinson's Disease

T. Lewis, B. Calamini, L. Verselis, M. Lowrey, L. Shaughnessy, J. Deranick, M. Dieter, M. Krautkramer, O. Uspenskaya, J. Sevigny (New York, USA)

Meeting: 2024 International Congress

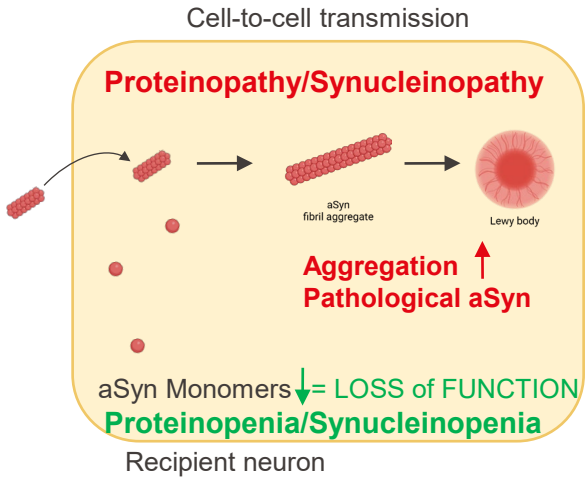
A Clinical Trial of LY3962681 in Healthy Volunteers and in Patients With Parkinson's Disease

Share study information

About the study

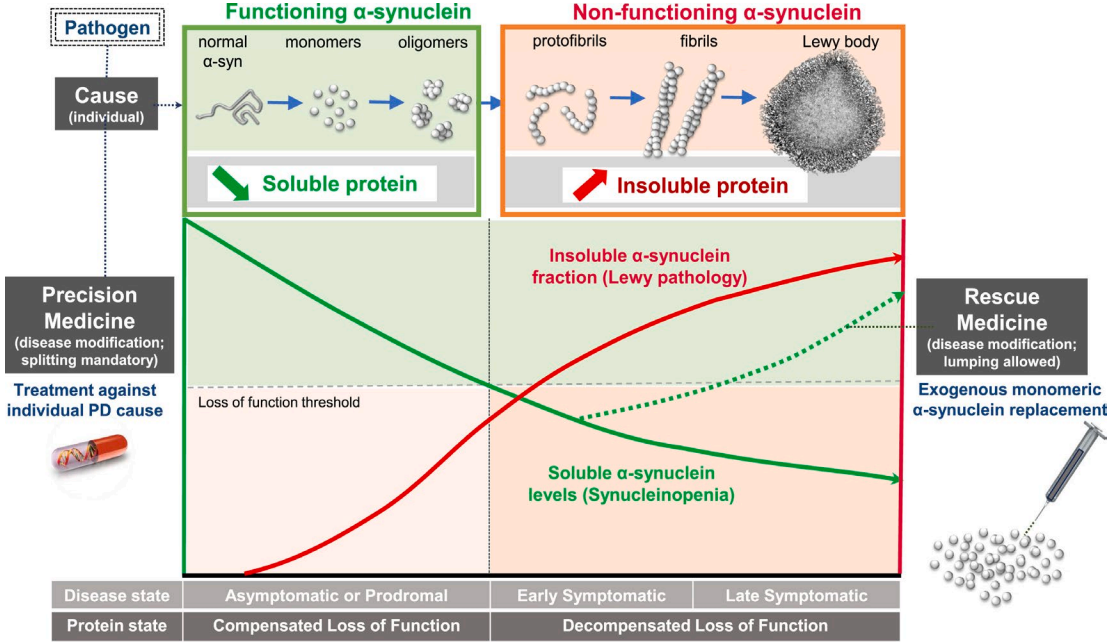
Actual Start Date: Aug 27, 2024	Estimated Primary Completion Date: May 5, 2029	Last Update Date: Oct 18, 2024
Study Status: Recruiting	Study Type: Interventional	Phase: Phase 1
Conditions: Parkinson's Disease	Enrollment: 108	Additional

Controversy around endogenous aSyn: Proteinopathy or Proteinopenia? ★



Alberto Espay · 2nd

Professor of Neurology, Advocate of precision medicine in neurodegenerative diseases, co-founder of Regain Therapeutics, evaluating treatments to correct proteinopenia.



Espay et al., 2024

Controversy around endogenous aSyn: Proteinopathy or Proteinopenia? ★

Proteinopathy / Synucleinopathy

- **Proteinopathy**
  A disease caused by **abnormal accumulation, misfolding, or aggregation of proteins** inside or outside cells.
  Examples: Aβ/tau in Alzheimer's, aSyn in PD, TDP-43 in ALS.

- **E.g., Synucleinopathy (PD, DLB, MSA, PDD…)**
  A **specific proteinopathy** in which the pathological protein is **alpha-synuclein (aSyn)**.
  Characterized by aggregates such as Lewy bodies or glial cytoplasmic inclusions.

- **Key concept:** *Too much, misfolded, or aggregated protein ➔ toxicity.*

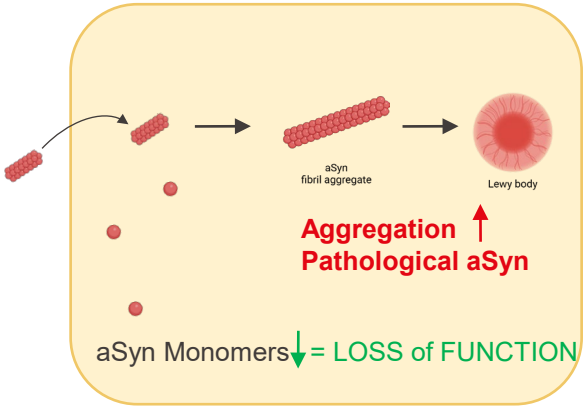
Proteinopenia / Synucleinopenia

- **Proteinopenia**
  A condition where a cell or tissue has **insufficient levels of a specific protein**, often leading to loss of normal function.
  (Not aggregation, but **deficiency**) Examples: Aβ/tau in Alzheimer's, aSyn in PD, TDP-43 in ALS.

- **Synucleinopenia (PD, DLB, MSA, PDD…)**
  A **specific proteinopenia** referring to **abnormally low levels of endogenous alpha-synuclein**.
  This may cause dysfunction because aSyn is involved in synaptic vesicle trafficking, neurotransmitter release, membrane dynamics (!!!! The true function of aSyn not yet fully understood)

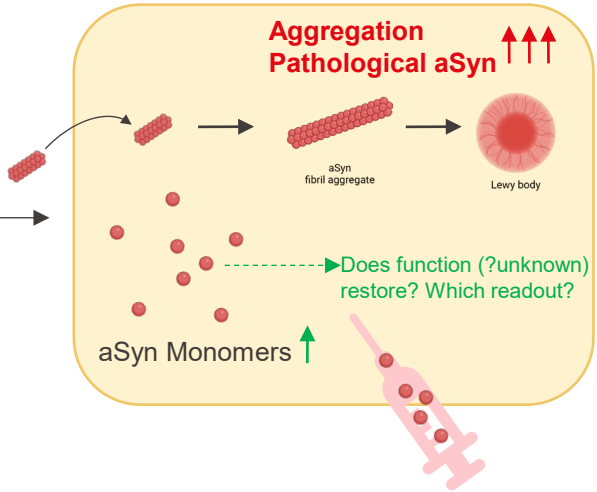
- **Key concept:** *Too little of the protein ➔ loss of essential physiological function ➔ toxicity*

Controversy around endogenous aSyn:
Shall we reduce or replace endogenous aSyn?★



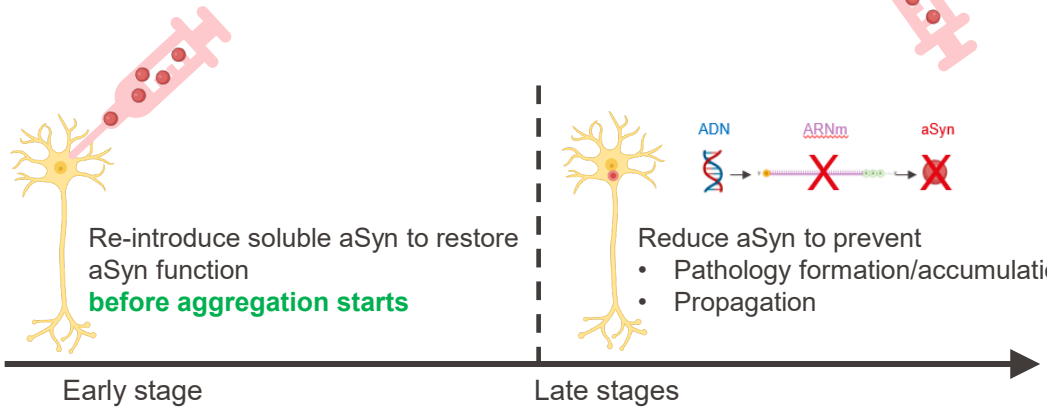
Therapeutic strategy

Re-introduce soluble aSyn



Alberto Espay · 2nd

Professor of Neurology, Advocate of precision medicine in neurodegenerative diseases, co-founder of Regain Therapeutics, evaluating treatments to correct proteinopenia.



Controversy around endogenous aSyn:

Shall we reduce or replace endogenous aSyn?
Proteinopenia or Proteinopathy?
Synucleinopenia or Synucleinopathy?

https://www.youtube.com/watch?v=CQM6V4Z4Fes

Controversy around endogenous aSyn:

Shall we reduce or replace endogenous aSyn?
Proteinopenia or Proteinopathy?
Synucleinopenia or Synucleinopathy?

1. Lewy pathology does *not* always correlate with PD ★

-No direct correlation between number of Lewy bodies and neuronal loss

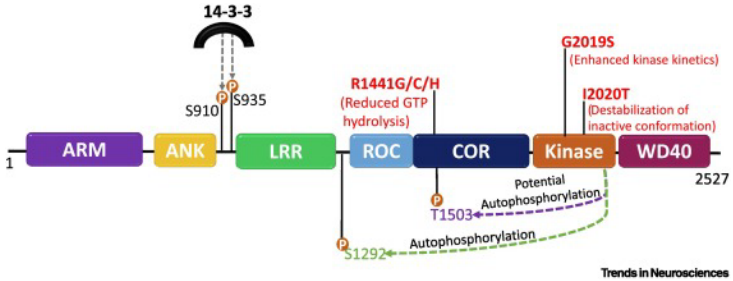
-Some young cases not related to PD have incidental Lewy bodies without symptoms

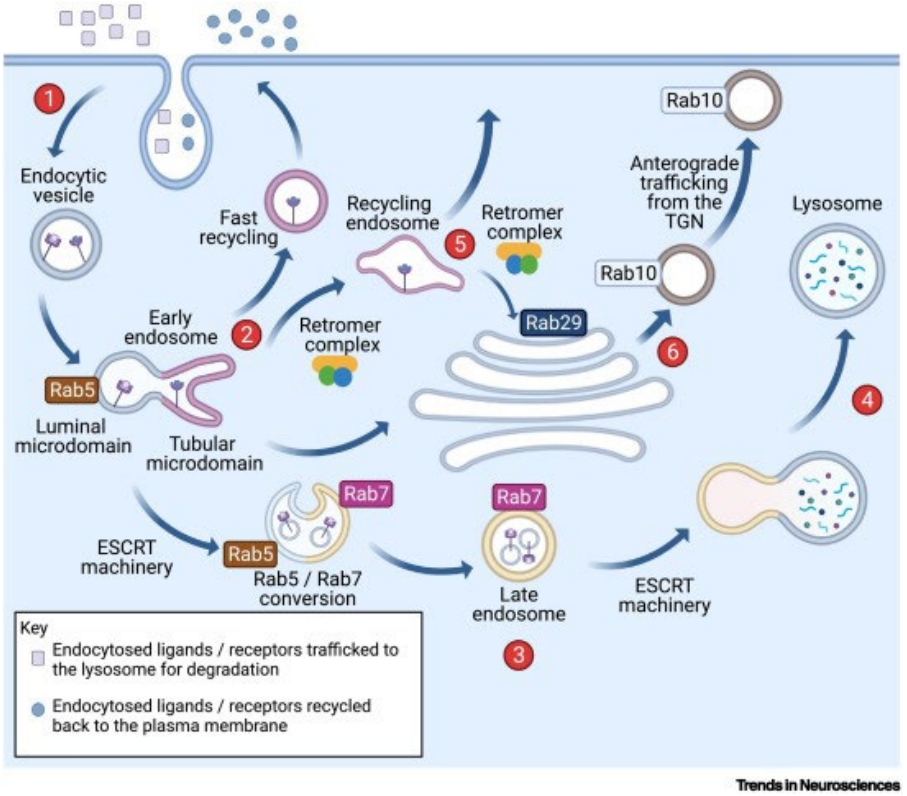
-Lewy pathology can be found in elderly individuals with **no PD or DLB**

2. "PD without Lewy pathology" exists — especially in LRRK2 mutation carriers ★

- ~30% of LRRK2 mutation carriers show **no Lewy pathology** at autopsy
- Parkin mutation carriers also show in ~80% the absence of Lewy bodies

Controversy around endogenous aSyn:
The case of the LRRK2 patients





https://www.cell.com/trends/neurosciences/fulltext/S0166-2236%2821%2900250-2

Controversy around endogenous aSyn: ★
The case of the LRRK2 patients

LRRK2-associated Parkinson's disease is one of the most common genetic-linked forms of PD, yet a large proportion of mutation carriers show *no Lewy pathology* at autopsy.
This challenges the classical model in which aSyn aggregation is the central driver of neurodegeneration.
Several explanations have been proposed:

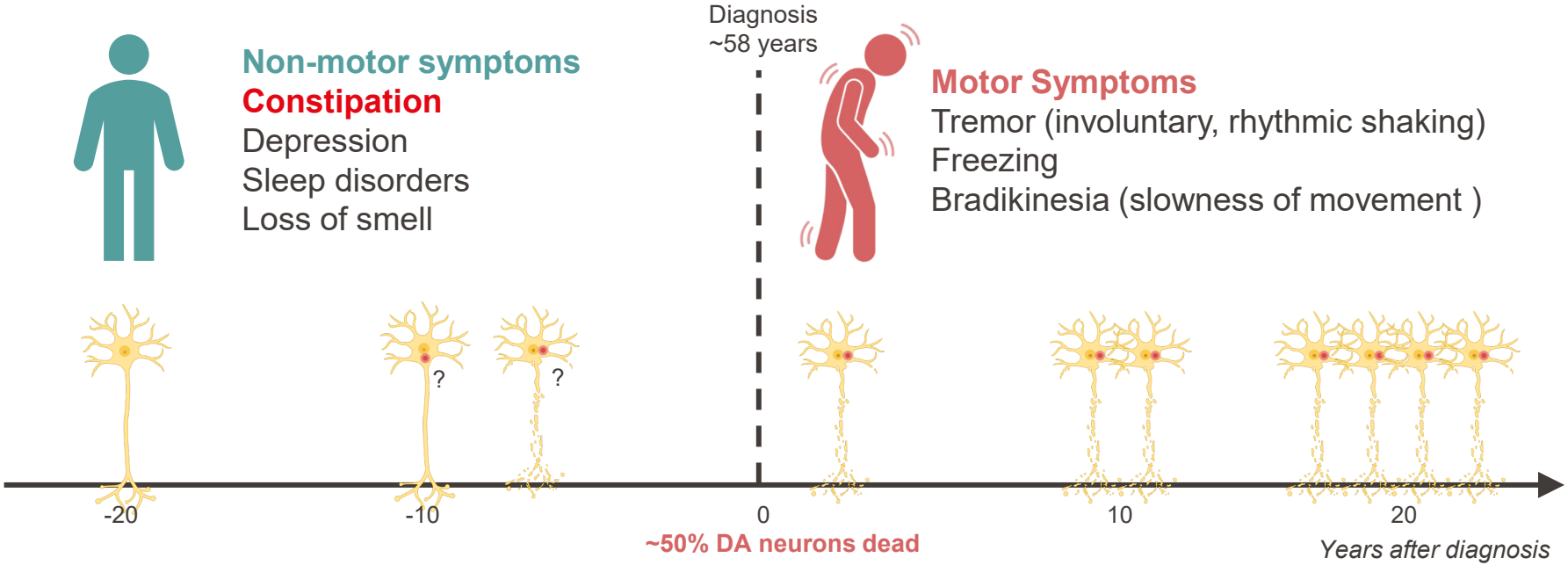
1.Neurodegeneration may occur through aSyn-independent mechanisms.
LRRK2 mutations affect vesicle trafficking, lysosomal function, mitochondrial homeostasis, and immune pathways, any of which can cause neuronal vulnerability without requiring Lewy bodies.

2. aSyn may be present but structurally different and undetectable with standard tools.
Some LRRK2-PD cases may harbor atypical aSyn species that do not bind conventional markers such as pS129 antibodies. Truncation? PTMs? Requirement to have specific antibodies to detect the pathology?

3.Pathology may involve non-fibrillar, oligomeric aSyn forms.
These toxic species are invisible to most histological methods and may accumulate despite the absence of classical Lewy bodies.

Together, these findings show that LRRK2-PD represents a distinct biological subtype of PD.
It highlights the need for:
– **better biomarkers** that detect diverse α-syn species
– **patient-specific therapeutic strategies**
– recognition that **no single aSyn-targeting therapy will fit all patients**

Mapping the landscape of heterogeneity in Parkinson's Disease :
From patients to the cellular pathology of Lewy Bodies



Parkinson's Disease:
Brain first vs. body first hypothesis ★

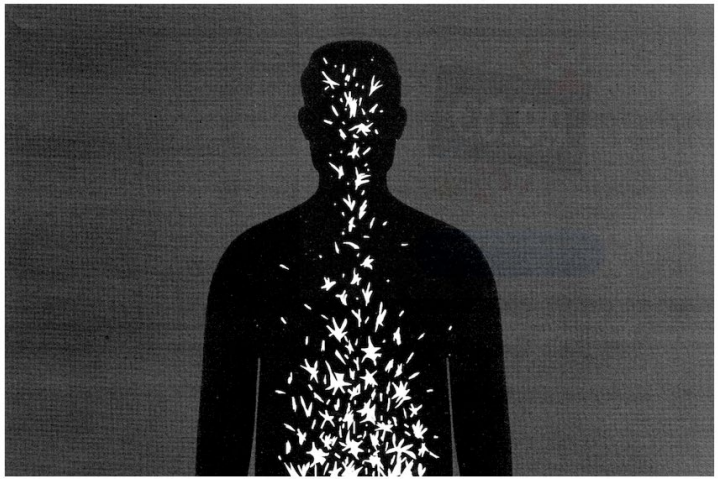
BRAIN MATTERS

Origins of Parkinson's may lie in the gut. Researchers hope to prove it.

If the hypothesis that misfolded proteins start in the gut and travel to the brain is proved, it could lead to early detection and treatment of Parkinson's

By Meeri Kim

September 28, 2023 at 6:00 a.m. EDT

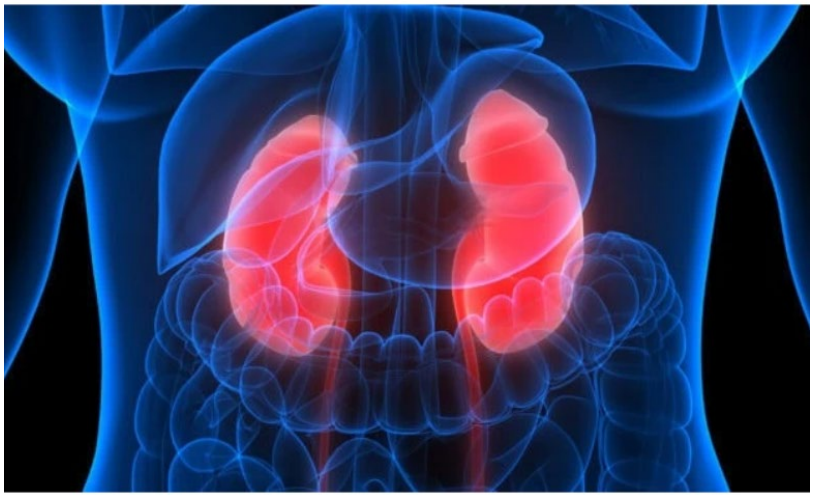


(George Wylesol for The Washington Post)

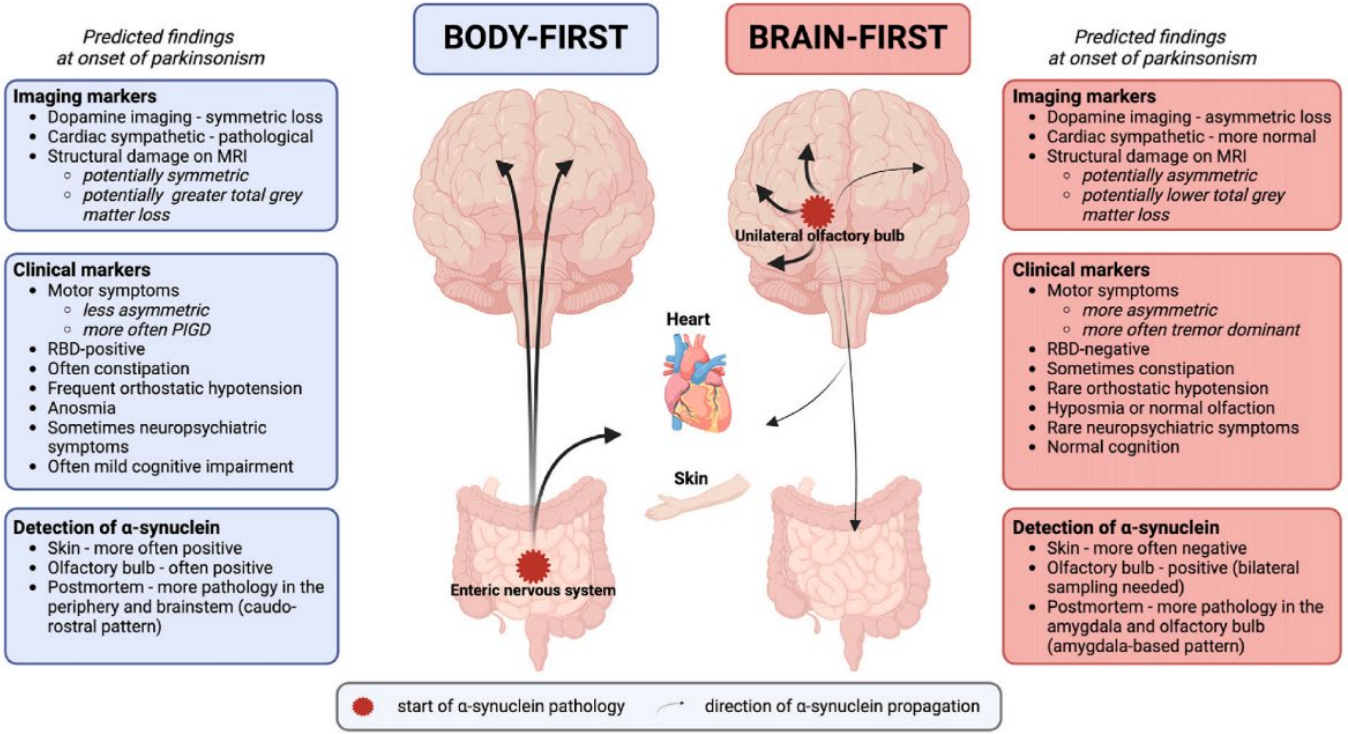
Scientists uncover kidney-to-brain route for Parkinson's-related protein spread

by Eric W. Dolan — June 22, 2025 in Neuroimaging, Parkinson's disease

https://www.nature.com/articles/s41593-024-01866-2



Mapping the landscape of heterogeneity in Parkinson's Disease : From patients to the cellular pathology of Lewy Bodies ★

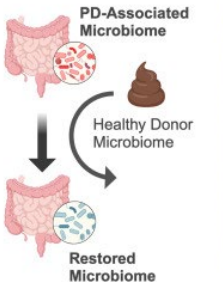


https://www.sciencedirect.com/science/article/pii/S1353802024001135

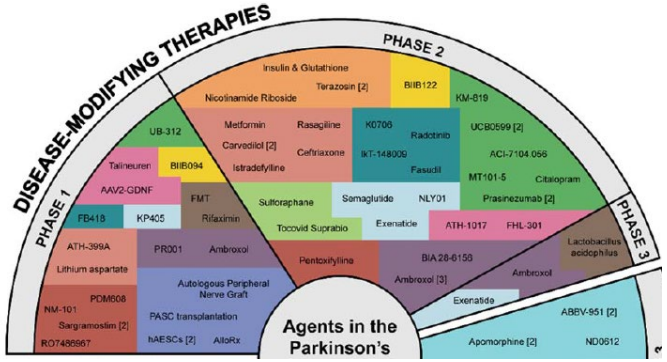
POV therapeutic strategy: If PD starts in the **brain**, treatment must focus on **protecting neurons**. If it starts in the **body**, we must **block disease propagation** before it reaches the brain.

Origin of the prion-like diseases – case of the PD

Microbiome-based therapeutics in recent and ongoing studies ★

	Fecal Microbiota Transplant (FMT)	Probiotics & Prebiotics	Emerging Alternatives
Approach		**Probiotics:** Lactobacillus Bifidobacterium Bacterial Cocktail **Prebiotics:**  Dietary fiber	**Antibiotics** **Polyphenols?**  **Phage?** **CRISPR?**  Editing microbiome
Notable Clinical Trials	1. Bruggeman et al., 2024 2. Scheperjans et al., 2024 3. DuPont et al., 2023 4. Cheng et al., 2023	1. Yang et al., 2023 2. Du et al., 2022 3. Hall et al., 2023 4. Becker et al., 2021	1. Rifaximin (NCT03575195) 2. Ceftriaxone (NCT03413384) 3. Erythromycin (NCT02005029)
Routes & Frequency of Admin	• Oral Delivery[3,4] ◦ 1x wkly, 3 wks[4] ◦ 2x wkly, 12 wks[3] • Nasojejunal, single [2] • Colonic, single [1]	• Oral Delivery[1-4] ◦ Daily[1-4] ◦ 10 days[3] ◦ 8-12 weeks[1,2,4]	• Oral Delivery[1] ◦ 2 wks – Freq NA • Intramuscular[2] ◦ Triweekly – 2 wks • I.V. – single admin[3]
Treatment Properties	• Donor Stool: ◦ Pooled[3] ◦ Single donor[1,2,4]	• Lactobacillus & Bifidobacterium[1,2] • Fiber preparations[3,4]	• Rifaximin[1] • Ceftriaxone[2] • Erythromycin[3]
Major GI Outcomes	• ↓ Constipation[1,3,4] • ↓ Gut transit[1] • No effect[2]	• ↓ Constipation[1,2] • ↓ GI inflammation[3,4]	• In progress: ◦ Not tested[1,2] ◦ Gastric Emptying[3]
Major Motor Outcomes	• ↓ UPDRS scores[1,3,4] • ↓Motor deficits[3] • ↓ Falls[3] • No effect[2]	• No effect[1] • Not tested[2-4]	• In progress: ◦ UPDRS scores[1-3] ◦ DAT SPECT[2] ◦ Motor function[3]

Hamilton et al., 2024



Microbiome/GIT(6%)

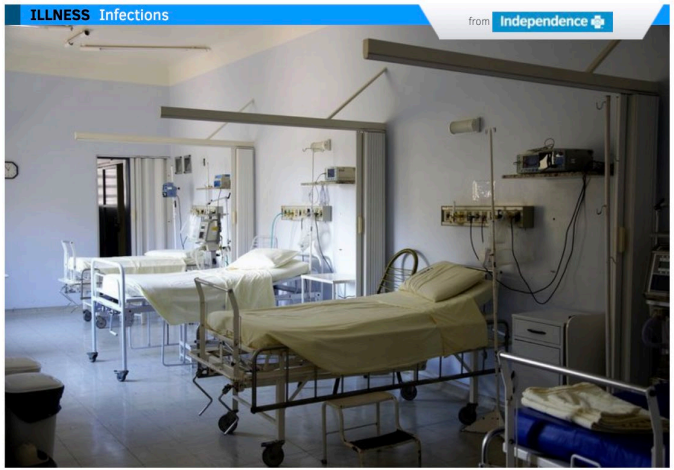
Origin of the prion-like diseases – case of the PD

Fecal microbiota transplantation

This treatment for an intestinal infection sounds disgusting, but it may be a breakthrough, and it has FDA approval

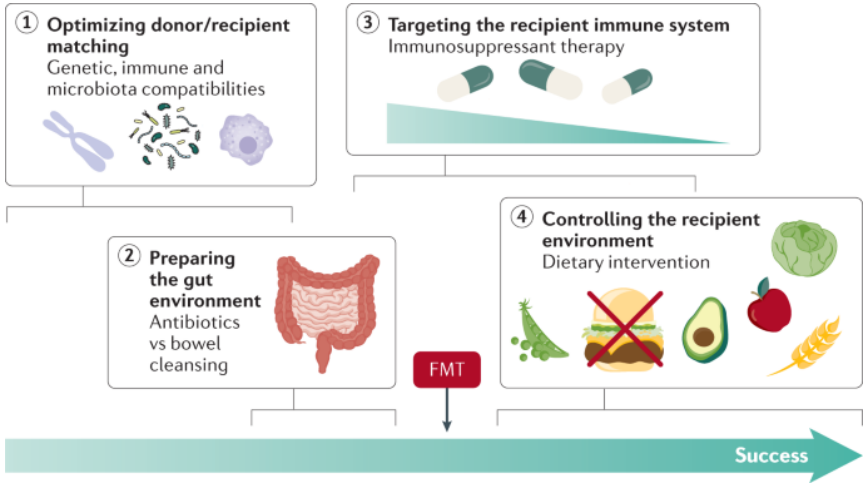
Vowst is a fecal matter transplant pill that is proving effective at treating C. diff, a potentially deadly illness most widespread among hospital patients

BY MICHAEL TANENBAUM
PhillyVoice Staff

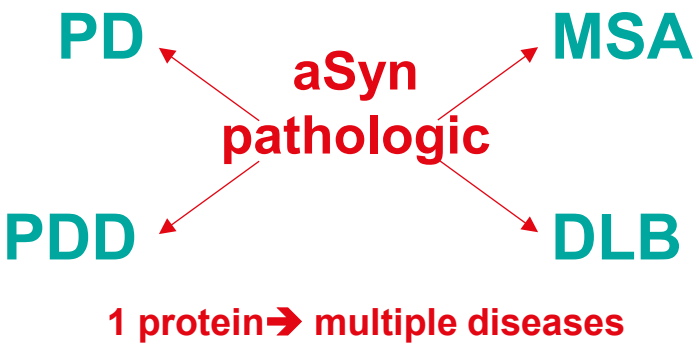


Recipient factors in faecal microbiota transplantation: one stool does not fit all

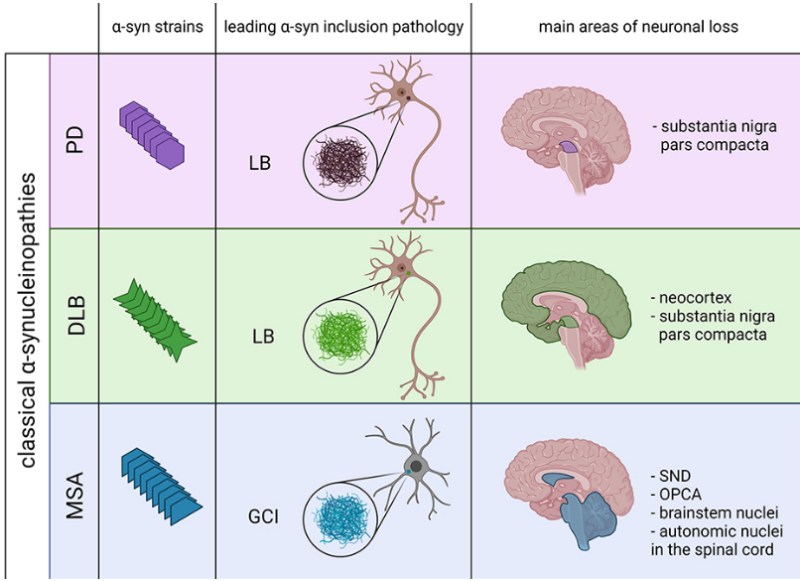
Camille Danne, Nathalie Rolhion and Harry Sokol



Mapping the landscape of heterogeneity in Parkinson's Disease :
From patients to the cellular pathology of Lewy Bodies★



1 protein➔ multiple diseases



https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.737195/full

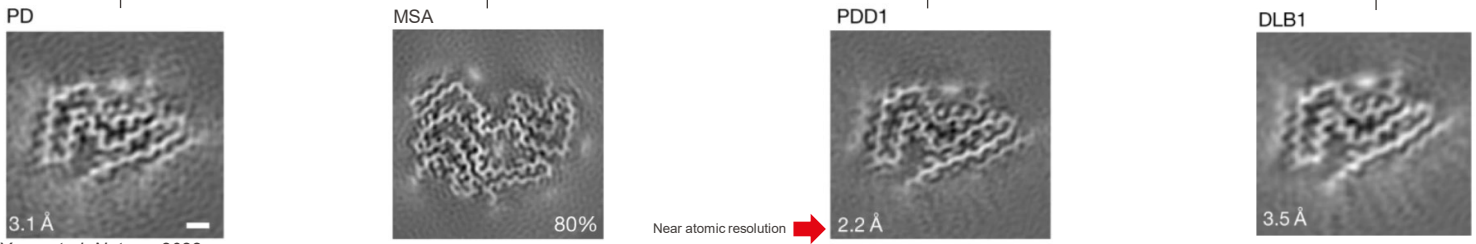
Mapping the landscape of heterogeneity in Parkinson's Disease : From patients to the cellular pathology of Lewy Bodies★

Synucleinopathies

PD MSA PDD DLB

Human tissues
From post-mortem patients

Biochemical Extraction of the **brain-derived fibrils/pathology** + **CryoEM** to decipher the structure



Yang et al, Nature, 2022
Scheiwgauser et al., 2020

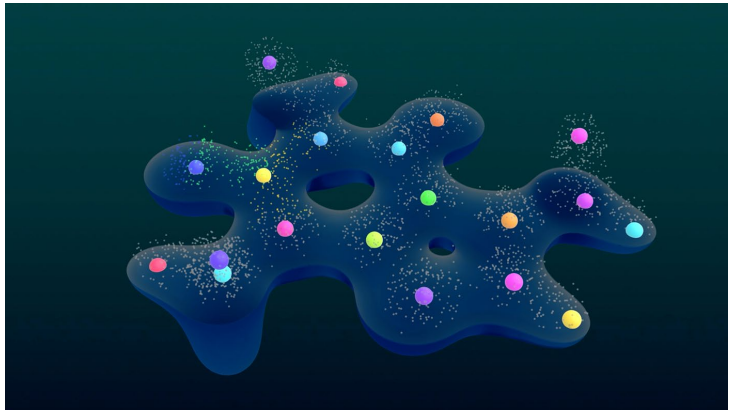
It is not only WHERE but also HOW the protein misfolds that matters in the synucleinopathies.

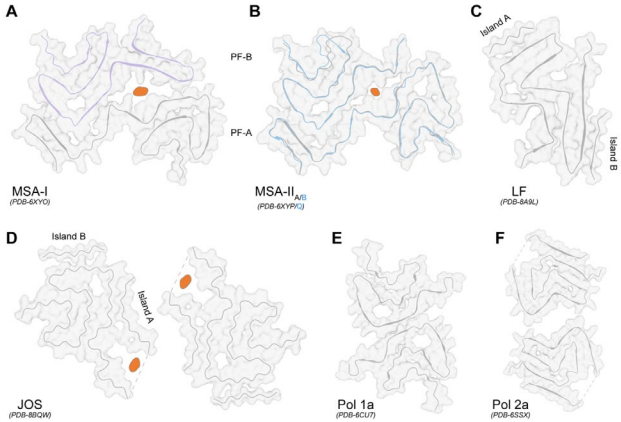
1 protein, multiple structural conformation – The concept of strains

Implication for Drug discovery – Strain-derived therapies? ★

Mapping the Structural Landscape of Amyloid Fibrils to Guide Polymorph-Specific Therapeutics

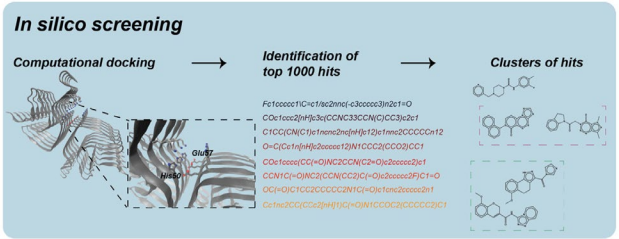
Ahmed Sadek[1,2], Bruno E. Correia[2#], Hilal A. Lashuel[1, 3, 4#]





Structure-Based Discovery of Small-Molecule Inhibitors of the Autocatalytic Proliferation of α-Synuclein Aggregates

Sean Chia, Z. Faidon Brotzakis, Robert I. Horne, Andrea Possenti, Benedetta Mannini, Rodrigo Cataldi, Magdalena Nowinska, Roxine Staats, Sara Linse, Tuomas P. J. Knowles, Johnny Habchi, and Michele Vendruscolo*

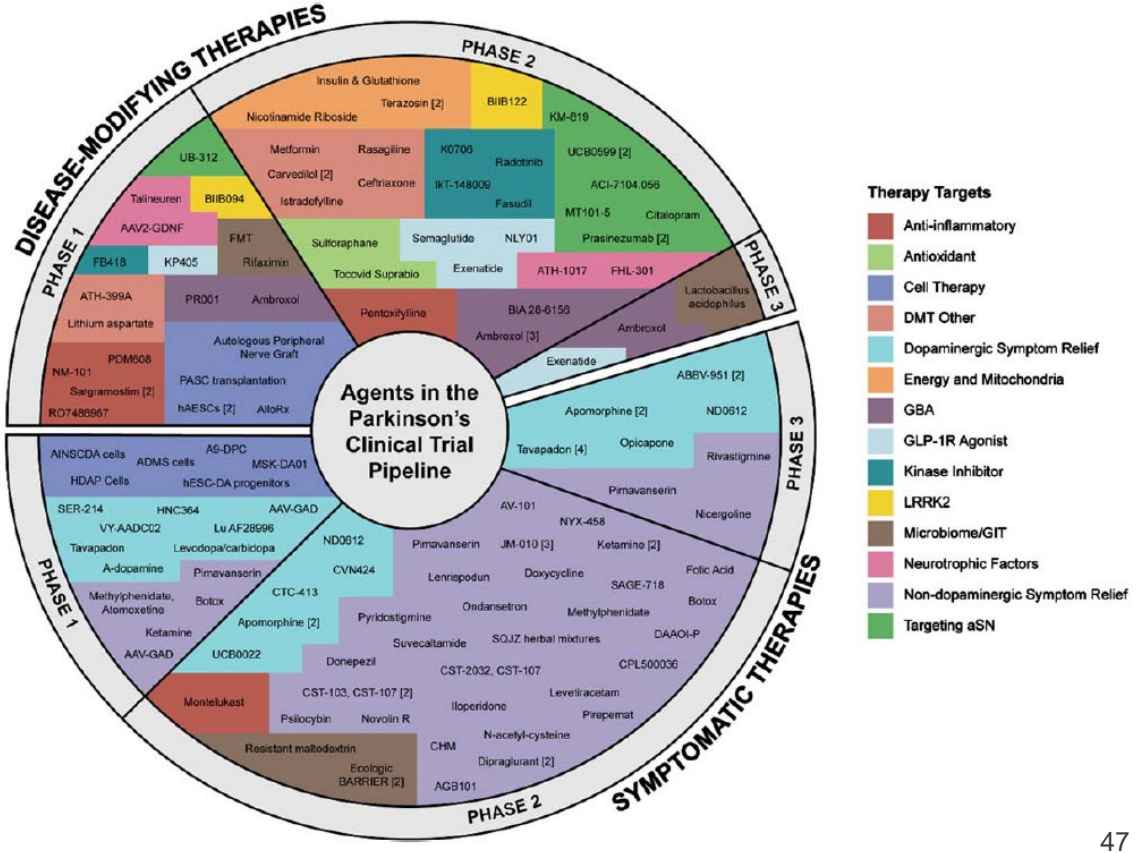


POV Therapeutic strategies: which part of the protein to target with antibodies or small molecules ?★

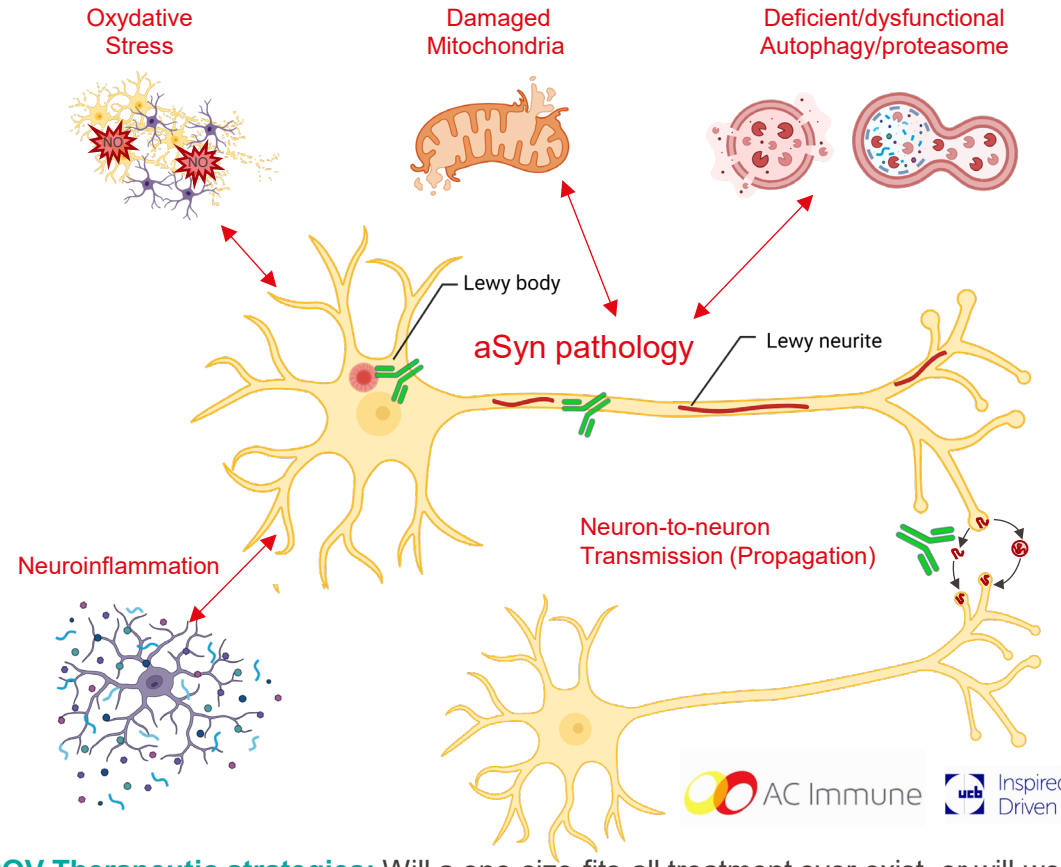
Drug therapies against PD and associated disorders:
On going clinical trials

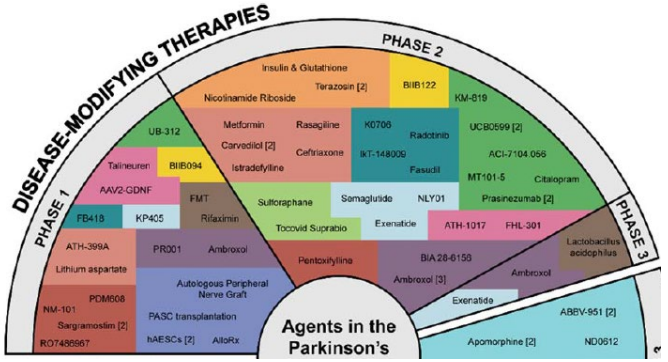
Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

Kevin McFarthing[a], Sue Buff[b], Gary Rafaloff[c], Kenneth Pitzer[d], Brian Fiske[e], Anaya Navangul[f], Katelyn Beissert[f], Aleksandra Pilcicka[f], Rosie Fuest[f], Richard K. Wyse[f] and Simon R.W. Stott[f,*]



Drug therapies against PD and associated disorders: ★
On going clinical trials





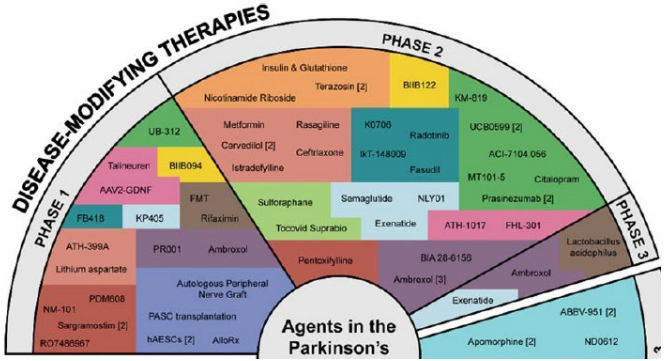
- Targeting aSyn (14%)
- Clearance (6%)
- Energy and mitochondria (6%)
- Anti-Oxydant (6%)
- Anti-inflammatory (10%)
- LRRK2 (4%)
- GBA and clearance (6%)
- GLP1-R(6%)
- Cell therapy (8%)
- DMT other (14%)
- Neurotrophic factor (8%)
- Microbiome/GIT(6%)

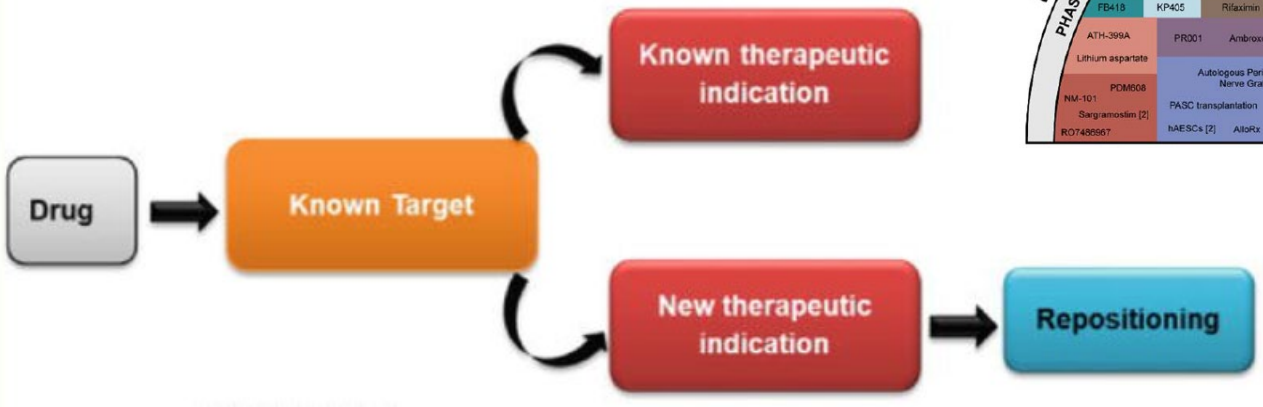
AC Immune · ucb Inspired by patients. Driven by science. · Roche

POV Therapeutic strategies: Will a one-size-fits-all treatment ever exist, or will we need to combine different therapeutic approaches?

PD Medications Currently in Clinical Trials – 2024

Case of drug repurposing ★

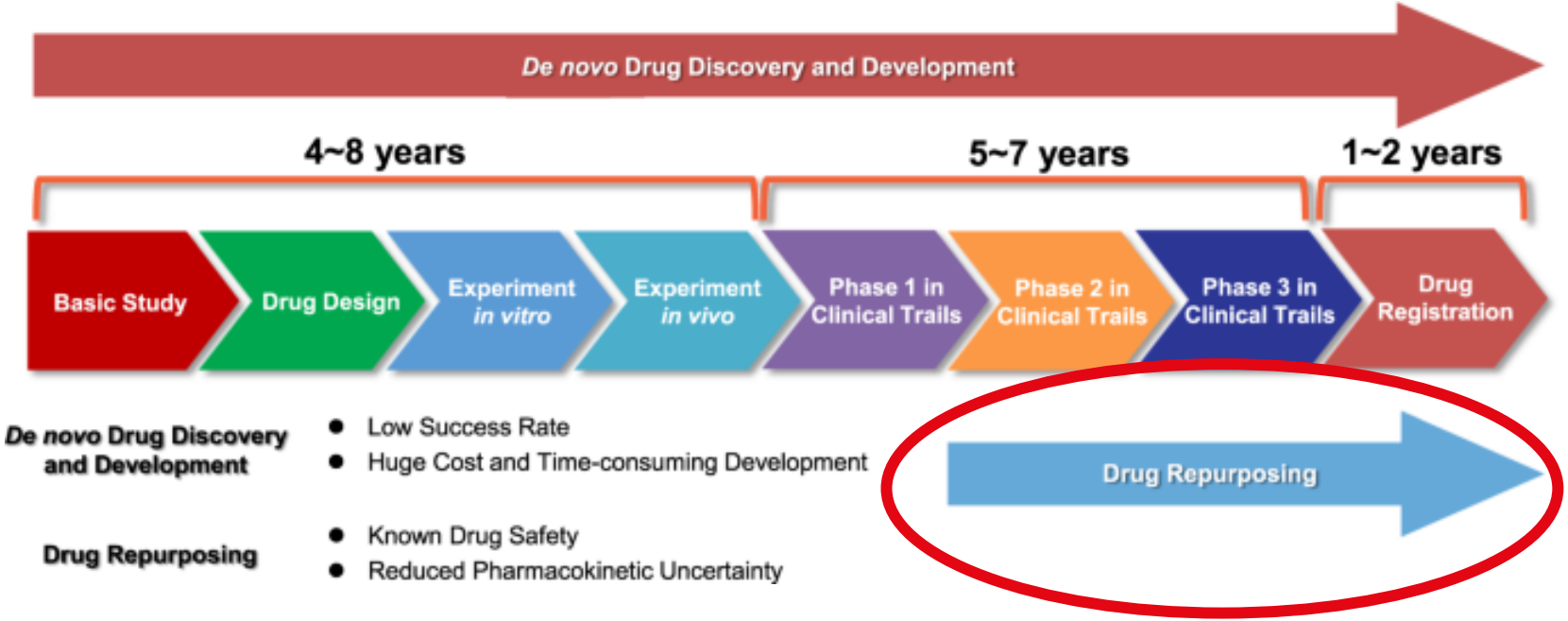




GLP1-R (6%)

PD Medications Currently in Clinical Trials – 2024

Case of drug repurposing



PD Medications Currently in Clinical Trials – 2024

Case of drug repurposing

What is the most famous examples of drug repurposing ?

Key Points on Viagra's repurposing:

•**Original purpose**:
Developed as a cardiovascular drug (sildenafil) to improve blood flow and reduce angina symptoms.

•**Repurposing discovery**:
During clinical trials, researchers observed its unexpected effect on erectile dysfunction (ED).

•**Approval for new use**:
Based on these findings, Pfizer reoriented its research, and in 1998, sildenafil was approved by the FDA as a treatment for ED.

•**Success and impact**:
Viagra became a widely recognized drug, generating billions in revenue and highlighting the potential of drug repurposing in uncovering new therapeutic applications.

PD Medications Currently in Clinical Trials – 2024

Case of drug repurposing ★

Drug repurposing is a medication originally developed and approved for one disease or condition but later found to be effective in treating another, different disease.

The advantages of drug repurposing include:

1. Reduced development time: repurposed drugs have already undergone preclinical and early-stage clinical testing, which can **save years** in development time compared to new drugs.

2. Lower costs: since many **safety and pharmacology studies** have already been **completed**, the overall cost is significantly lower than developing a new drug from scratch.

3. Known safety profile: repurposed drugs have established **safety data**, which reduces the risk of adverse side effects and allows researchers to focus more on efficacy for the new indication.

4. Broadening therapeutic applications: repurposing allows researchers to explore **new ways** to address complex or multi-faceted diseases, such as cancer or neurodegenerative disorders, often leading to combination therapies. E.g: GLP-1 receptor

7. Economic incentives: repurposing **can extend the commercial life of older drugs**, offering economic benefits for pharmaceutical companies, especially when **patent extensions or new intellectual property protections** can be established.

PD Medications Currently in Clinical Trials – 2024

Case of drug repurposing drug – GLP1 receptor (Diabetes type II)

156 patients 12 months study
Phase II in clinical trial – April 2024

ORIGINAL ARTICLE

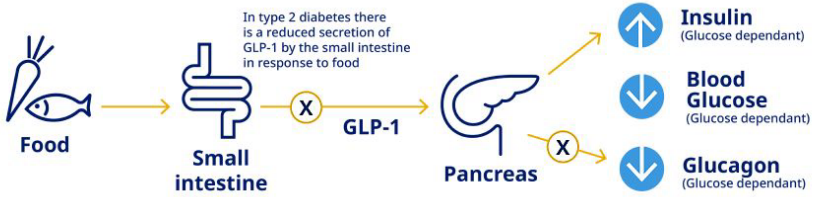
Trial of Lixisenatide in Early Parkinson's Disease

W.G. Meissner, P. Remy, C. Giordana, D. Maltête, P. Derkinderen, J.-L. Houéto, M. Anheim, I. Benatru, T. Boraud, C. Brefel-Courbon, N. Carrière, H. Catala, O. Colin, J.-C. Corvol, P. Damier, E. Dellapina, D. Devos, S. Drapier, M. Fabbri, V. Ferrier, A. Foubert-Samier, S. Frismand-Kryloff, A. Georget, C. Germain, S. Grimaldi, C. Hardy, L. Hopes, P. Krystkowiak, B. Laurens, R. Lefaucheur, L.-L. Mariani, A. Marques, C. Marse, F. Ory-Magne, V. Rigalleau, H. Salhi, A. Saubion, S.R.W. Stott, C. Thalamas, C. Thiriez, M. Tir, R.K. Wyse, A. Benard, and O. Rascol, for the LIXIPARK Study Group*

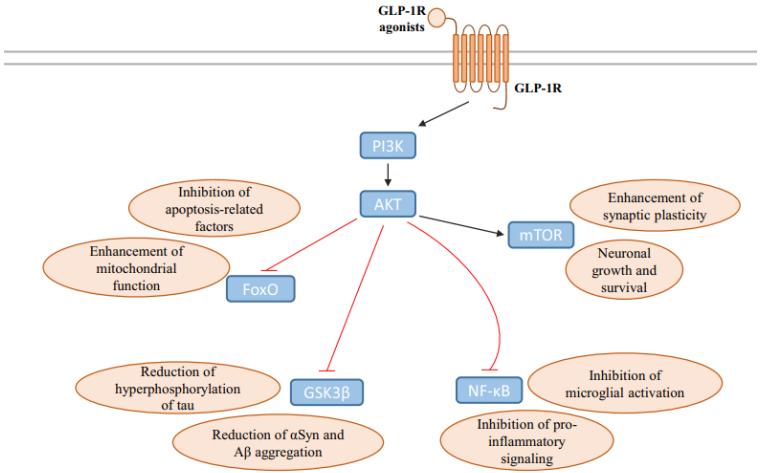
- Encouraging results (slowing of motor symptom progression over a one-year period).
- However, this study needs to be validated in a larger cohort of patients and repeated to assess long-term benefits

PD Medications Currently in Clinical Trials – 2024

Case of drug repurposing drug – GLP1 receptor (Diabetes type II)



Diabetes type II: GLP-1 is a **gut hormone** that helps control blood sugar. GLP-1 medicines make the pancreas release **more insulin ➔ Better blood sugar control and** help with **weight loss**



Repurposing GLP-1 Receptor Agonists for Parkinson's Disease: Current Evidence and Future Opportunities

Daniella Balduino Victorino[1] · Mariana Nejm[1] · Marcia Guimarães-Marques[1] · Fulvio Alexandre Scorza[1] · Carla Alessandra Scorza[1]

UNDER INVESTIGATION

Patient stratification: A key challenge in NDDs ★

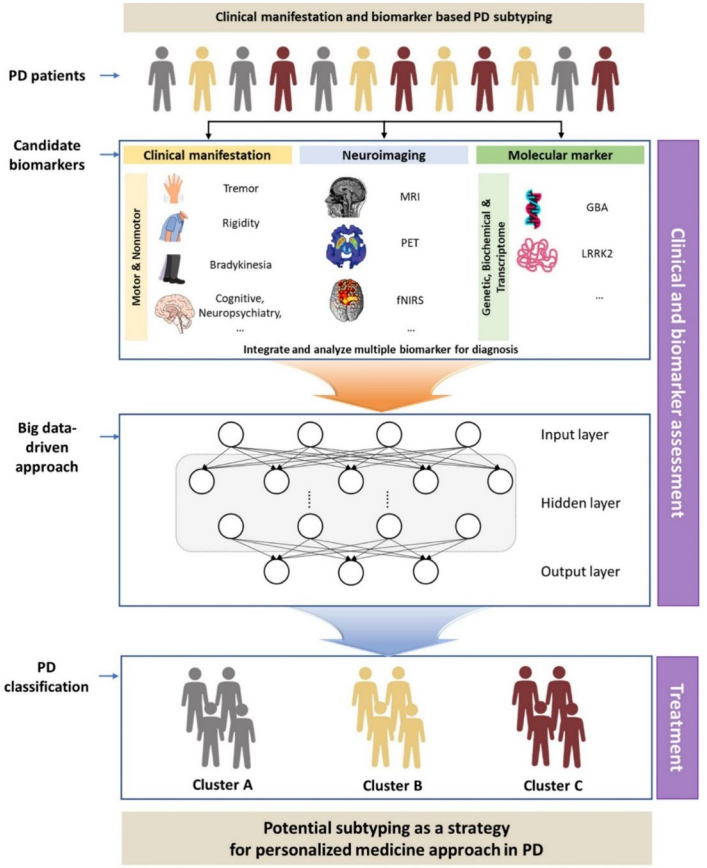
Optimizing cohorts to achieve more robust and meaningful clinical trial outcomes

To obtain more meaningful (and positive) clinical outcomes, it is essential to optimize patient cohorts by classifying individuals in a way that reflects the diversity and complexity of the neurodegenerative diseases.

How can we stratify patients?
Based on which specific criteria?

Age, motor and non-motor symptoms (constipation, REM sleep behavior disorder, loss of smell), and potential disease origin (brain-first vs gut-first)?

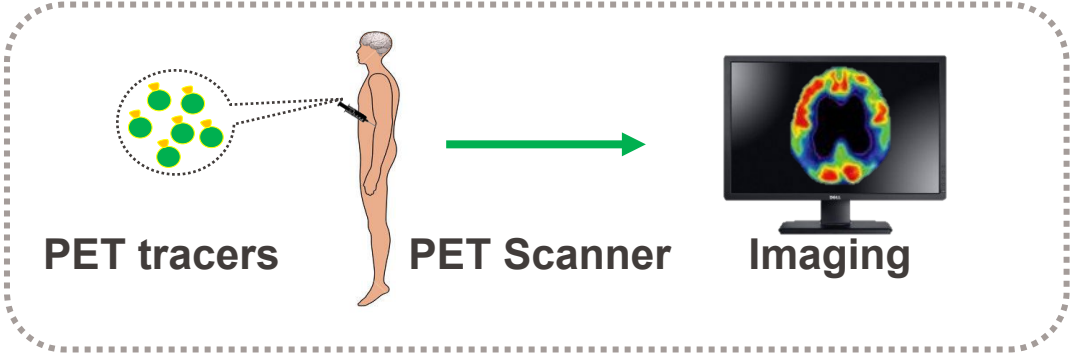
⚠ **A key point: Patient stratification is essential to accelerate the development of disease-modifying therapies and to ensure more robust and clinically relevant trial outcomes.**

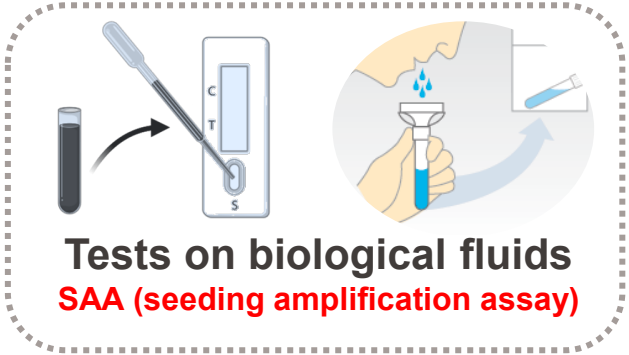


Seung Hyun Lee et al, 2022

Discovering new biomarkers:★

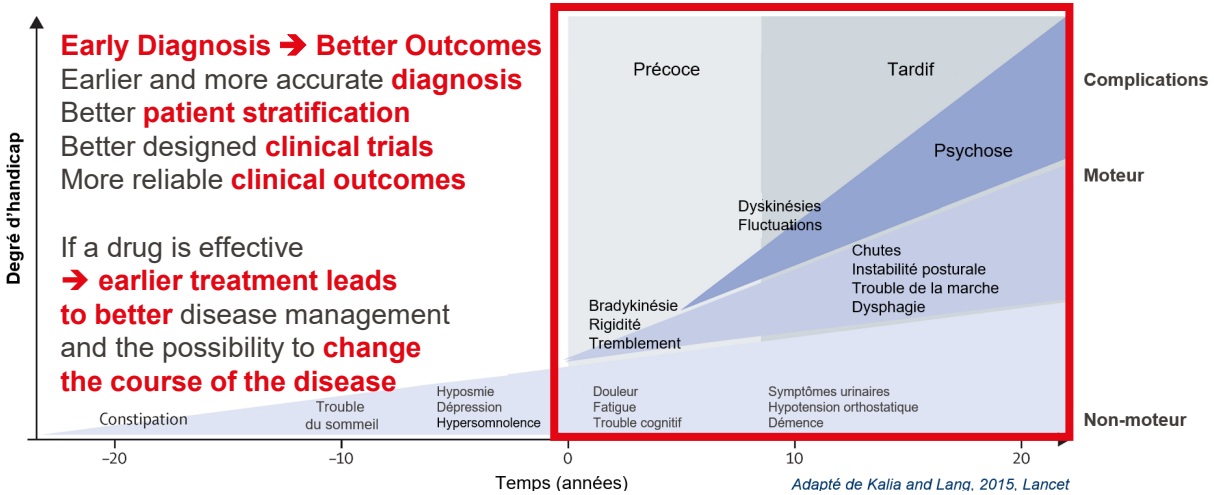
For earlier diagnosis and improved therapeutic effectiveness



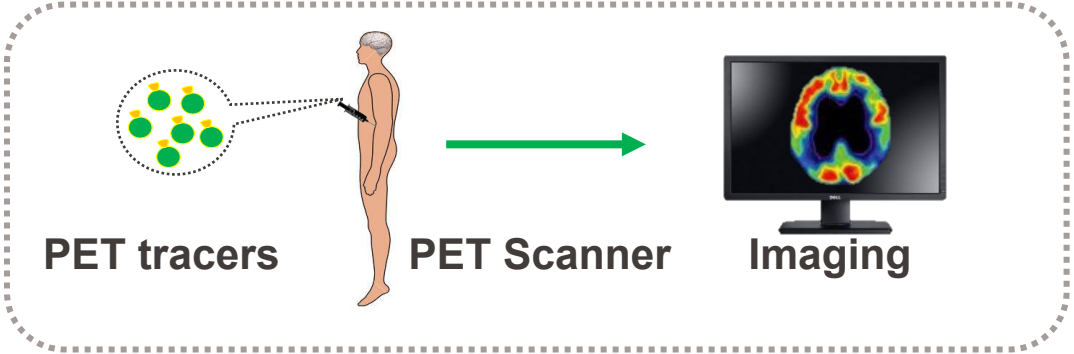


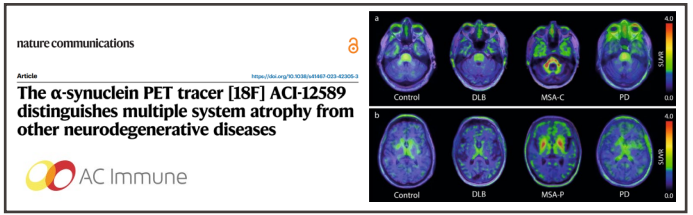
Early Diagnosis ➔ Better Outcomes
Earlier and more accurate **diagnosis**
Better **patient stratification**
Better designed **clinical trials**
More reliable **clinical outcomes**

If a drug is effective
➔ **earlier treatment leads to better** disease management and the possibility to **change the course of the disease**



Discovering new biomarkers:
For earlier diagnosis and improved therapeutic effectiveness





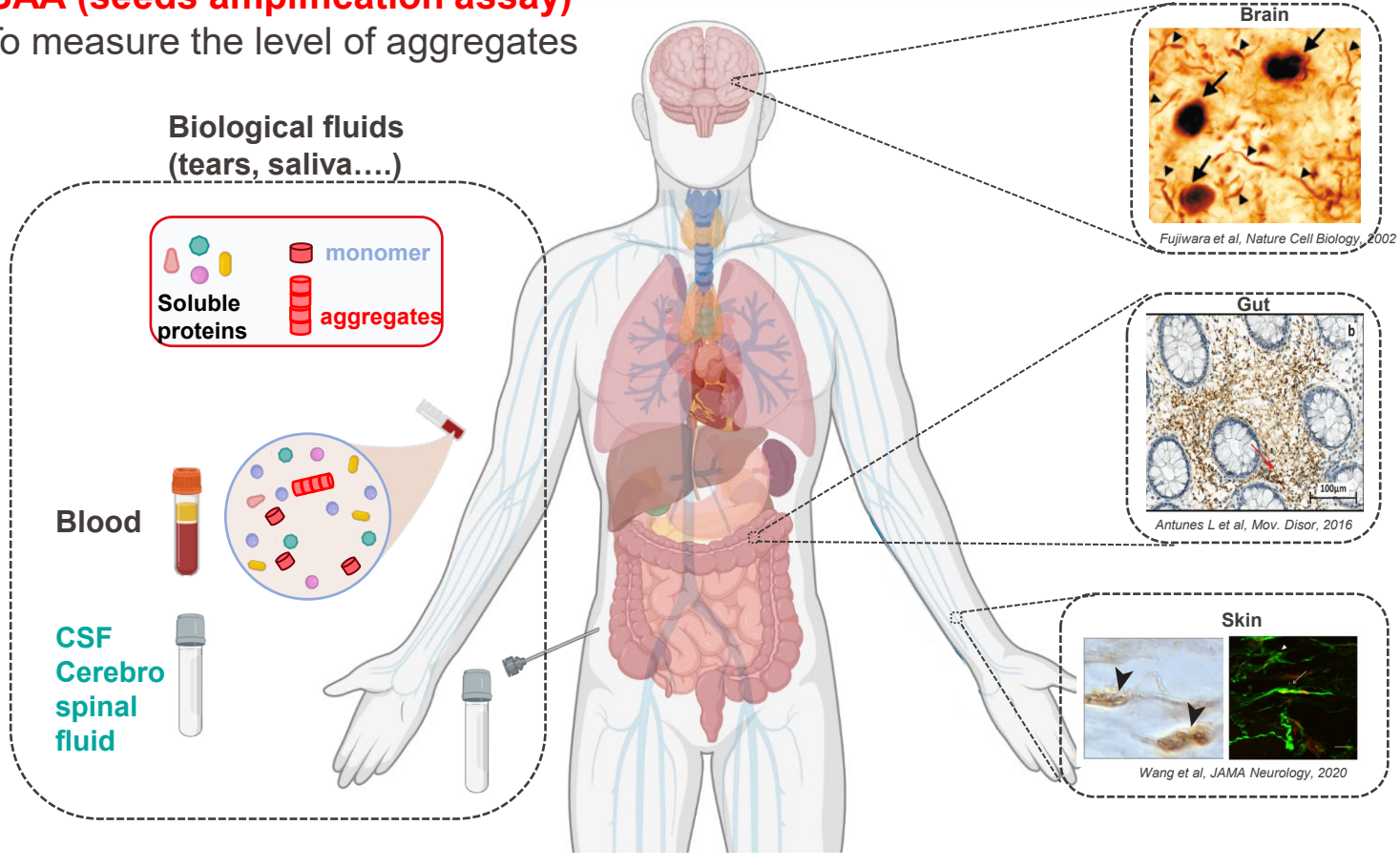
CLINICAL STAGE PROGRAMS

TARGET	PRODUCT CANDIDATE	INDICATION	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	PARTNER
alpha-synuclein	ACI-7104.056 *anti-a-syn active immunotherapy*	Parkinson's disease, alpha-synucleinopathies						AC Immune
	ACI-12589 *a-syn-PET[4] tracer*	Multiple system atrophy, alpha-synucleinopathies						AC Immune
	ACI-15916 *a-syn-PET[4] tracer*	Parkinson's disease, alpha-synucleinopathies						AC Immune

Prion-like aggregates: a new biomarker for early diagnosis ★

SAA (seeds amplification assay)

To measure the level of aggregates



Early diagnosis: The seeding amplification assay ★

CSF Cerebro spinal fluid

Can we dedect aggregates (aSyn, Tau, aβ) in body fluid ? And how ?

Hypothesis:
If body fluids contains aggregates, then these aggregates should still retain their prion properties and be able to seed monomeric proteins

Monomers	+	Seeds	=	newly formed aggregates

Early diagnosis: The seeding amplification assay ★

CSF Cerebro spinal fluid

Can we dedect aggregates (aSyn, Tau, aβ) in body fluid ? And how ?

Hypothesis:
If body fluids contains aggregates, then these aggregates should still retain their prion properties and be able to seed monomeric proteins

Monomers	+	Seeds	=	newly formed aggregates

Aggregates = seeds

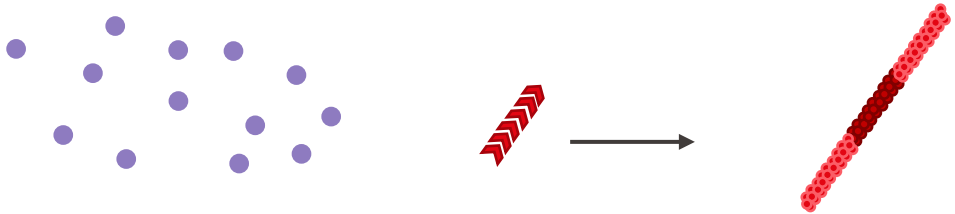
Early diagnosis: The seeding amplification assay ★

CSF Cerebro spinal fluid

Can we dedect aggregates (aSyn, Tau, aβ) in body fluid ? And how ?

Hypothesis:
If body fluids contains aggregates, then these aggregates should still retain their prion properties and be able to seed monomeric proteins

Monomers	+	Seeds	=	newly formed aggregates



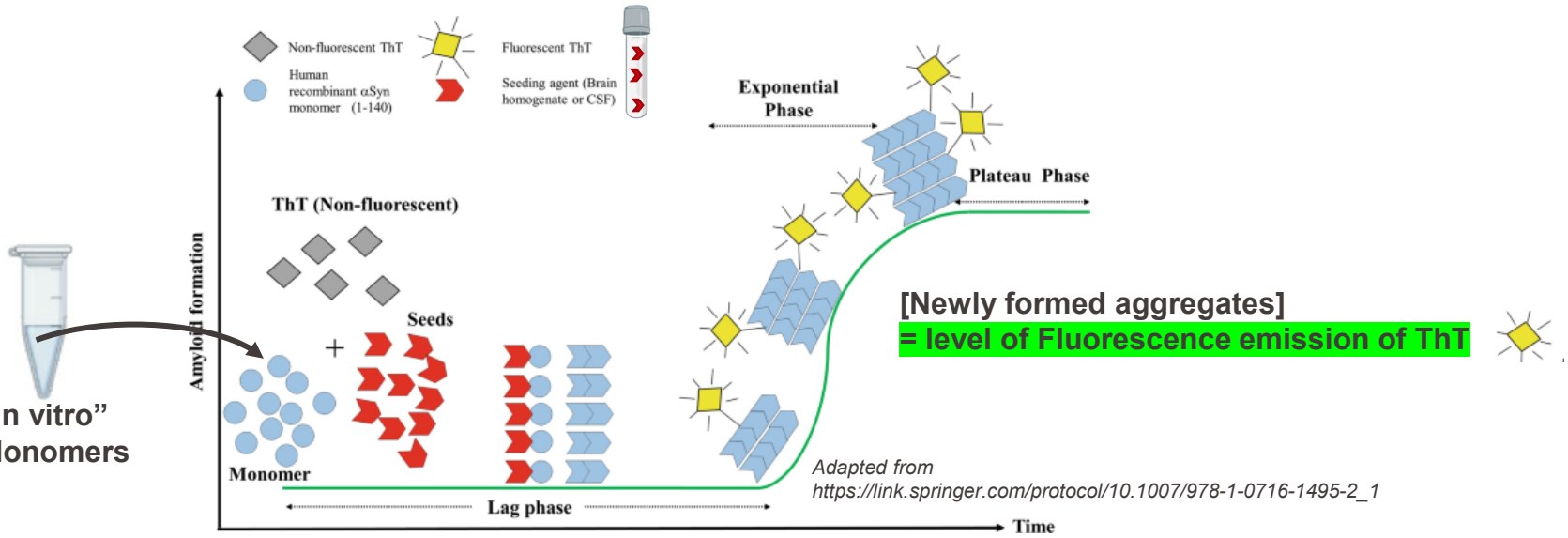
Early diagnosis: The seeding amplification assay ★

CSF Cerebro spinal fluid

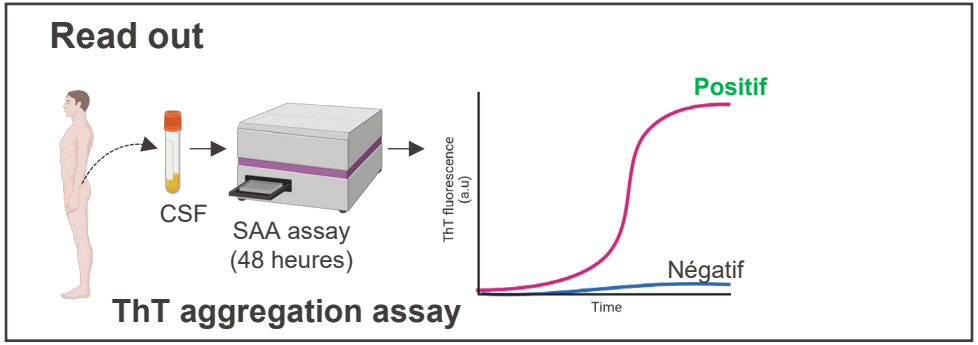
Can we dedect aggregates (aSyn, Tau, aβ) in body fluid ? And how ?

Hypothesis:
If body fluids contains aggregates, then these aggregates should still retain their prion properties and be able to seed monomeric proteins

Monomers	+	Seeds	=	newly formed aggregates



Early diagnosis: The seeding amplification assay ★



Patients with loss of smell

Group	CSF asyn SAA +
All PD	97% (548/567)
Sporadic PD	99% (402/407)
GBA PD	100% (59/59)
LRRK2 PD	85% (70/82)
SNCA PD	100% (11/11)
PRKN PD	50% (2/4)
HC	30% (8/26)

Patients without loss of smell

Group	CSF asyn SAA +
All PD	59% (114/193)
Sporadic PD	75% (90/120)
GBA PD	29% (2/7)
LRRK2 PD	34% (21/62)
SNCA PD	n/a
PRKN PD	50% (2/4)
HC	3% (6/179)

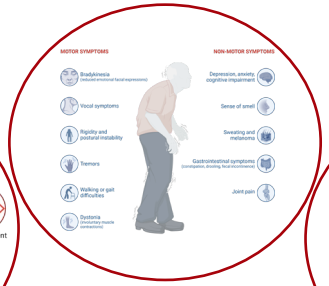
SAA has been acquired in 2428 PPMI participants https://www.ppmi-info.org/

Parkinson's Progression Markers Initiative

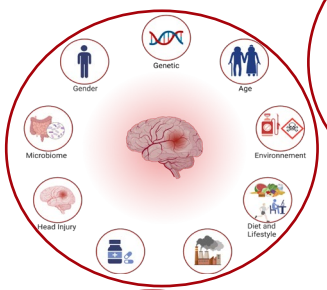
- Advantage: fast (<48h), cheap (<10$/plate), high-throughtput screening (386 well plates)
- Disadvantage: false positive level
- **If no DMT treatment, do the patients want to know 10-20 years before that they will have a NDD?**

Due to the heterogeneity and complexity of Parkinson's diseaseS, our approach must be integrated

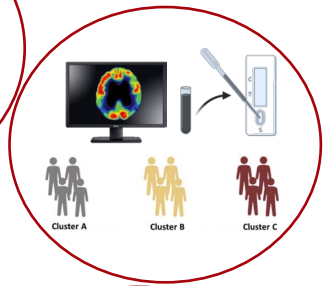
Complexity and diversity of symptoms



Prevent the disease
Risk factors

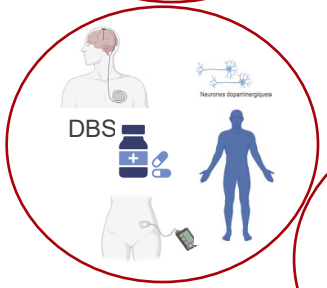


Diagnosis
Early and targeted
+ personalized medecine

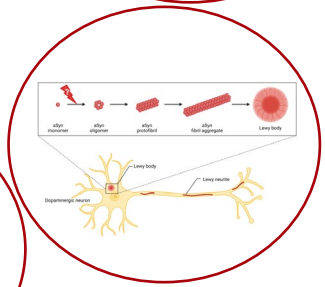


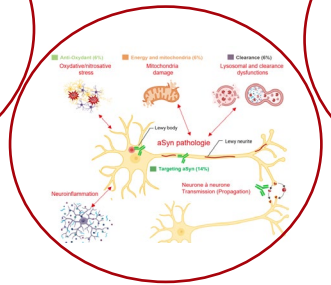
Integrated Approach

Treat
the symptoms



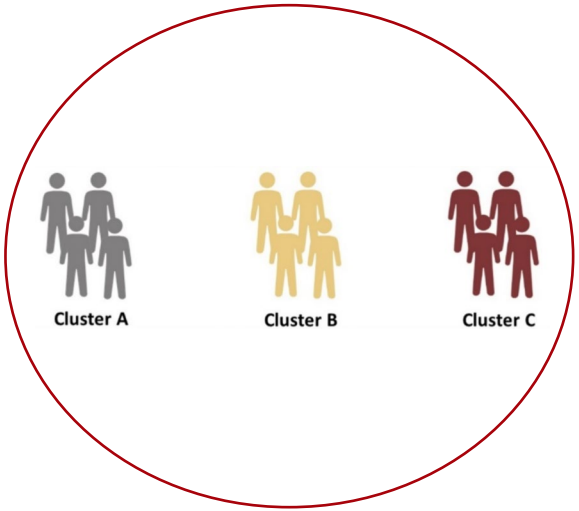
Understanding the biology of the pathology





Stopping or slowing disease progression (DMT)

Due to the heterogeneity and complexity of Parkinson's diseaseS, our approach must be integrated



Personnalised medecine

Lecture on the 12/12

Therapeutic strategies against synucleinopathies

See exercises in the Moodle

“**Therapeutic strategies against synucleinopathies**”

Any questions ? Or Thoughts ?