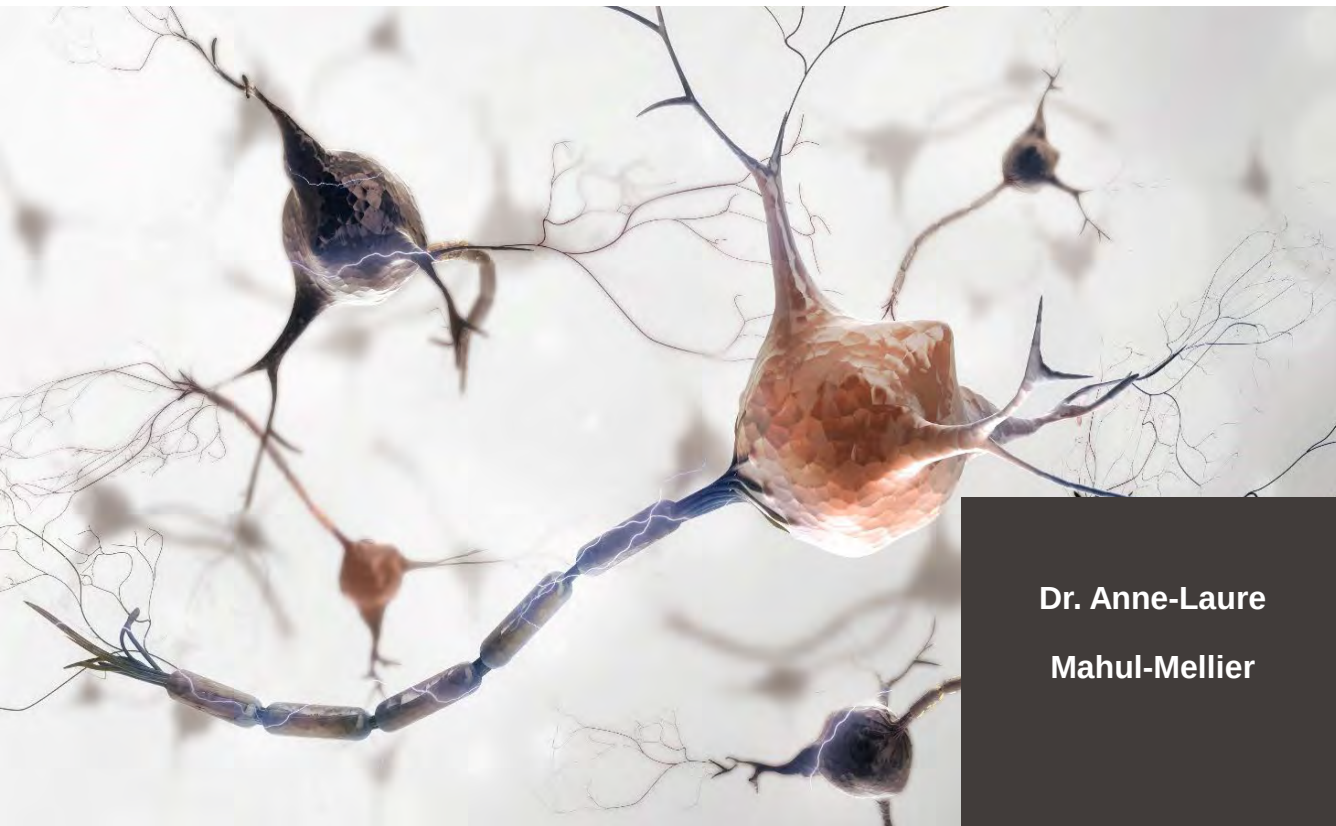
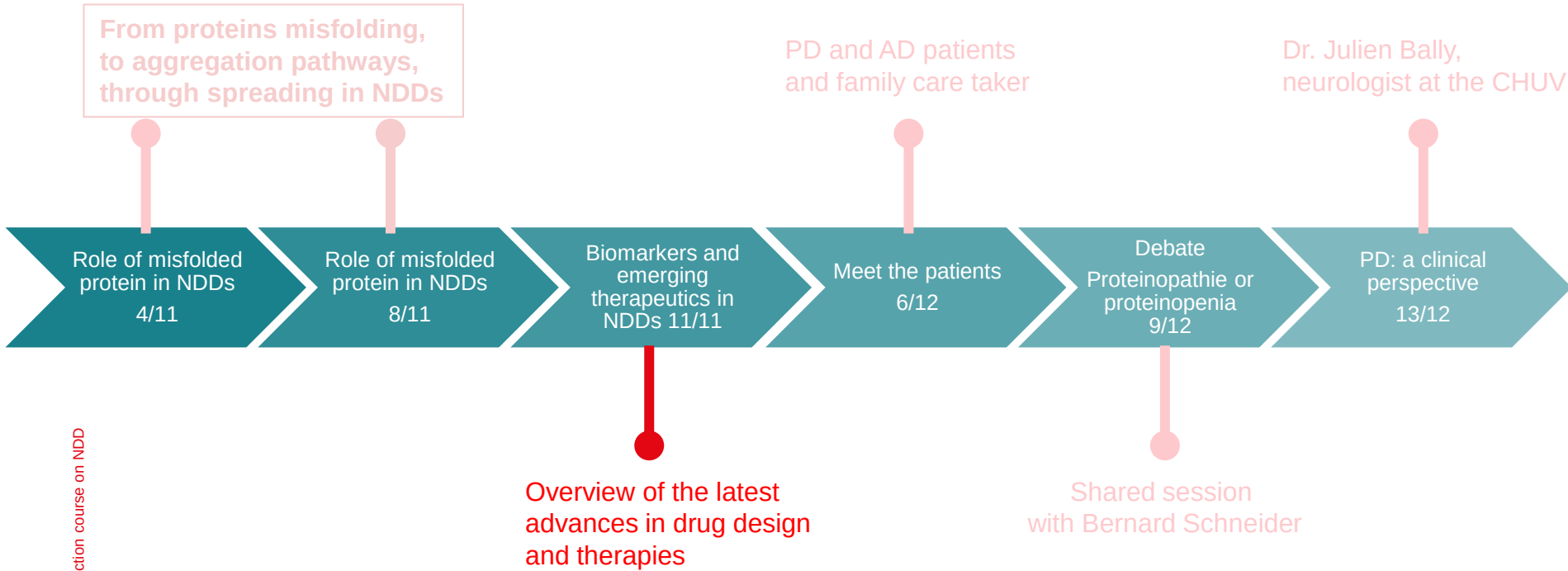




Welcome To Bi0480 – NDDs lectures 2024-2025

**Dr. Anne-Laure
Mahul-Mellier**

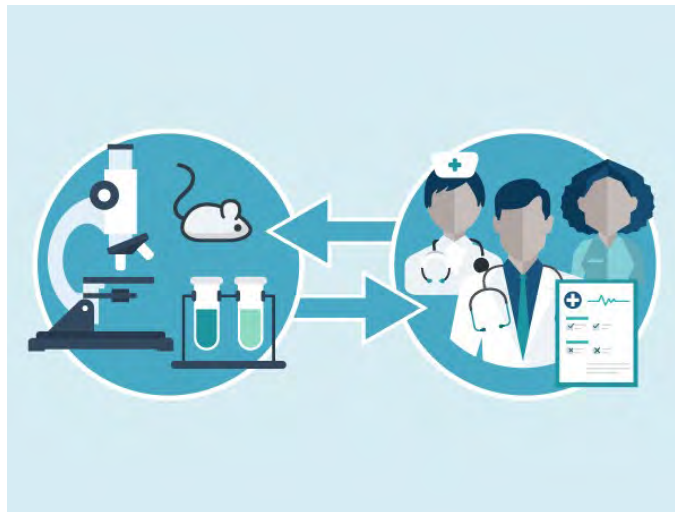


- I. Modeling neurodegenerative disorders (NDDs) in the Lab**
- II. Drugs therapy in Clinical trials**
- III. Bench techniques applied to early diagnosis**

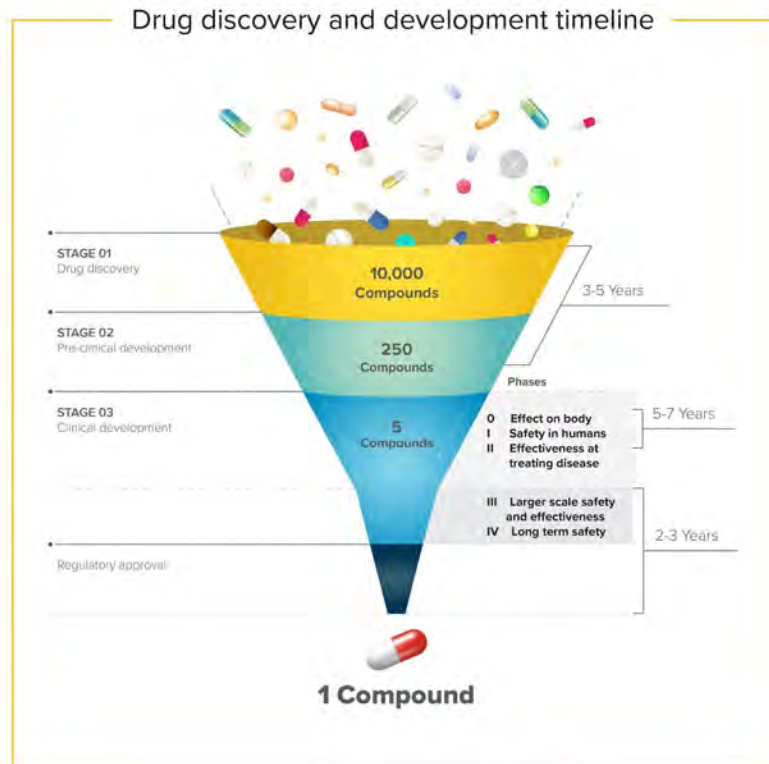
- I. **Modeling neurodegenerative disorders (NDDs) in the Lab**
- II. Drugs therapy in Clinical trials
- III. Bench techniques applied to early diagnosis

Modeling neurodegenerative disorders (NDDs) in the Lab: What does it matter ?

Implications for Therapeutic Strategies



Bench to Bedside: Translating Science from the lab to the Clinic

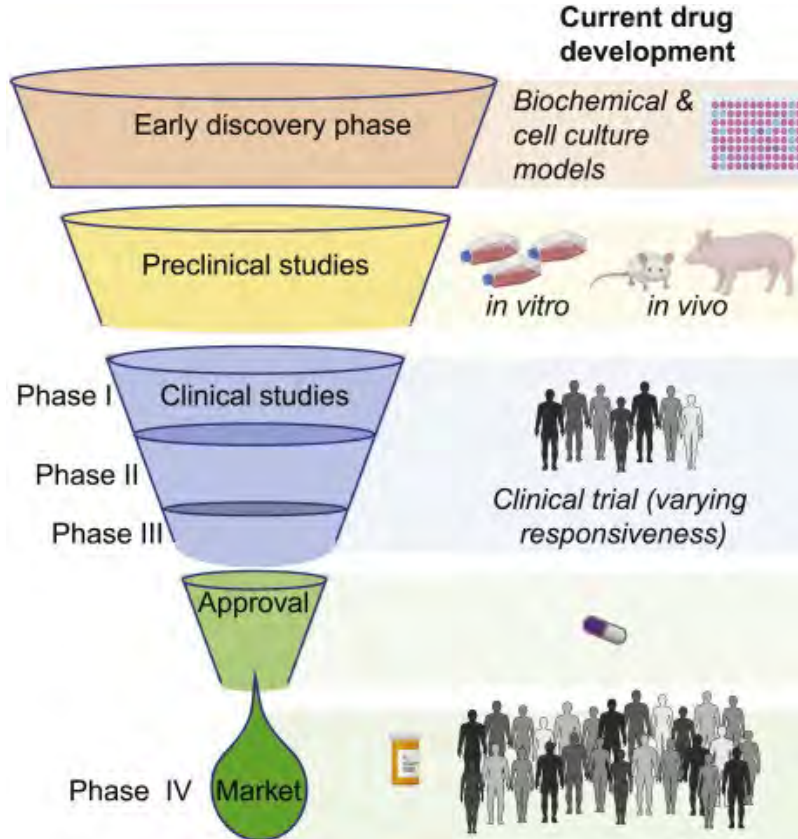


- The cost of developing a **new drug** that gets approval is estimated at around **\$2-3 billion**.
- Trials which **failed** at phase I or II wasted around \$6 million.
- Trial **failed** at phase III resulted in a loss of approximately \$77 million.
- The time it takes for an approved drug to reach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

Having the right model that mimic human pathology is fundamental for drug discovery

Bench to Bedside:

Translating Science from the lab to the Clinic



NO CURE

Or

Disease Modifying
Therapies

NO TEST

For early diagnosis



CAUSES UNKNOWN

Complex
and
Multi-factorial

- Lack of approved therapies to treat or slow the progression of the NDD
- Clinical trials of drugs/antibodies targeting protein aggregation continue to fail
- No early diagnosis for NDDs

Poor understanding of the cellular mechanisms responsible for the formation of protein inclusions found in patients

EPFL Lewy bodies in PD and Synucleinopathies: Cause or Consequence?

9



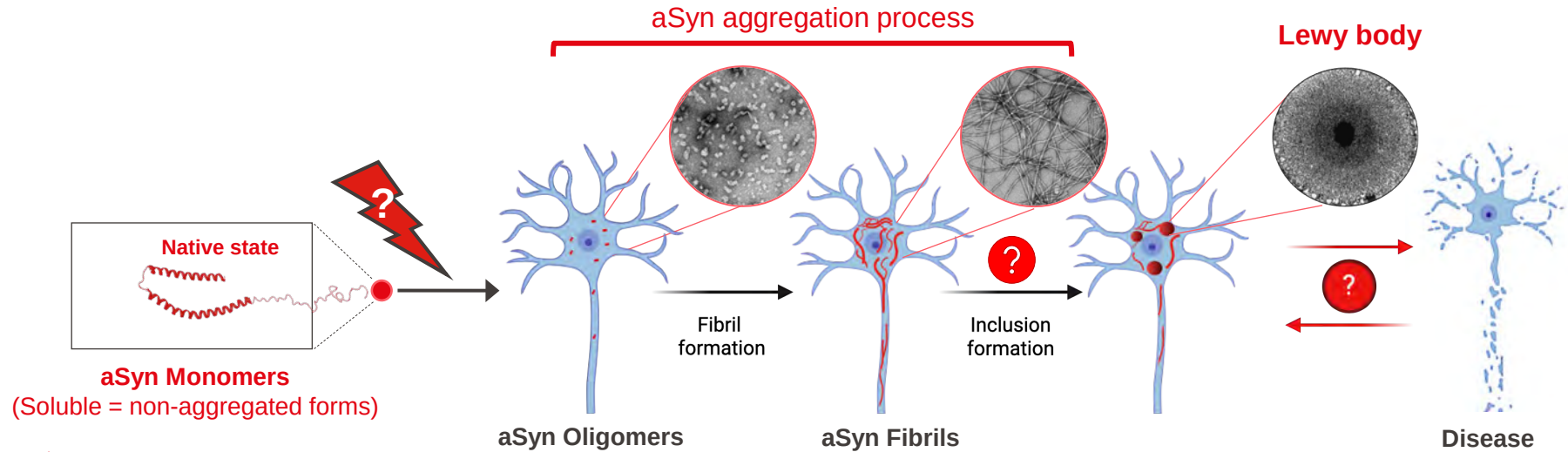
The level of LB pathology correlates with disease development, cognitive decline or disease progression and severity



Proteins aggregates are found in the brain of healthy individuals
Protein aggregates are absent in specific genetic forms of PD

**Answering this question requires the development of cellular or animal models
that recapitulates the process of LB formation**

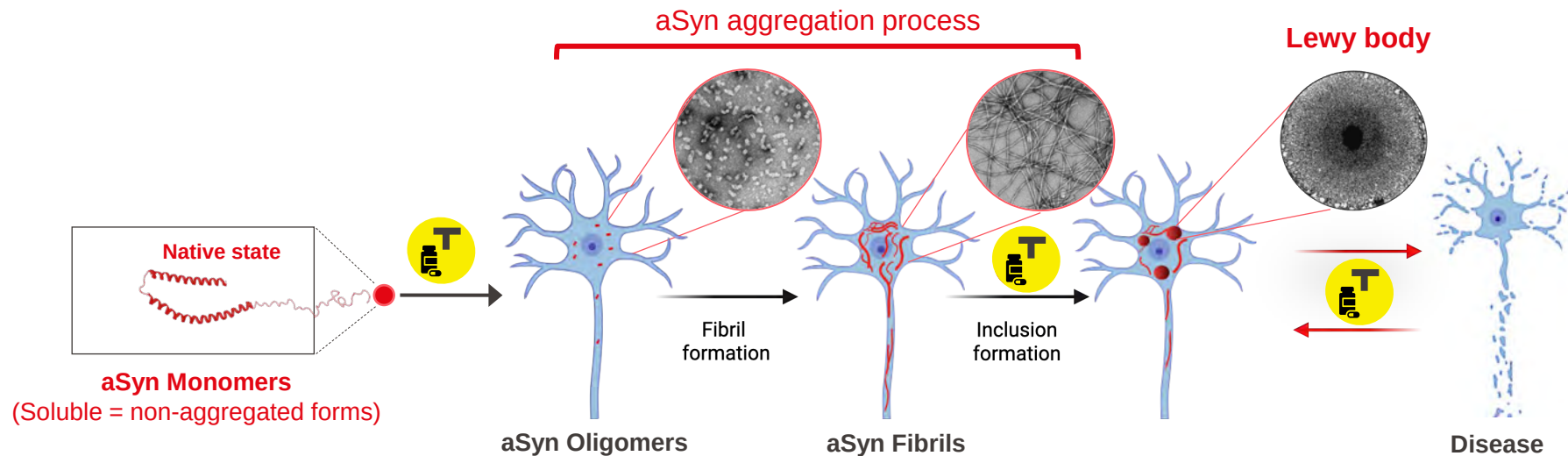
Preclinical models that accurately replicate the human pathology are essential



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

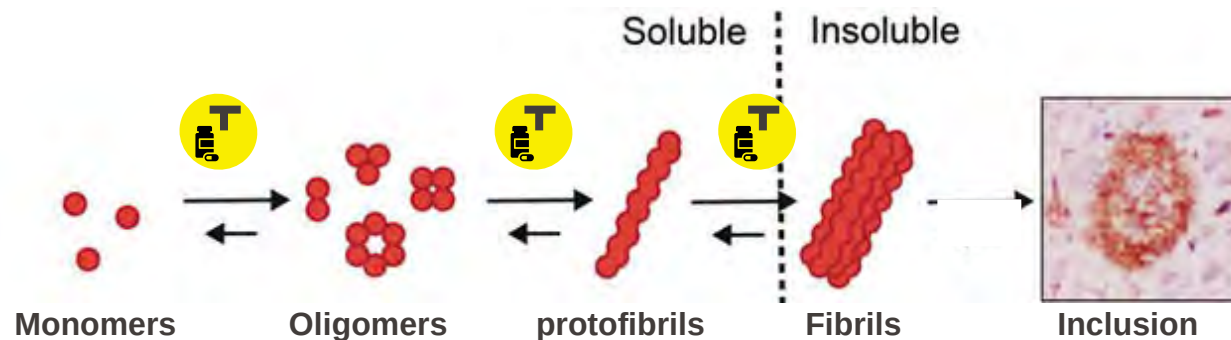
The ideal model of PD should enable to dissect all the steps leading to Lewy body formation and neurodegeneration.

Preclinical models that accurately replicate the human pathology are essential



Such models will enable to shed light on potential **therapeutic target** to develop **disease-modifying therapies**.

In vitro studies to understand the origin of the NDDs

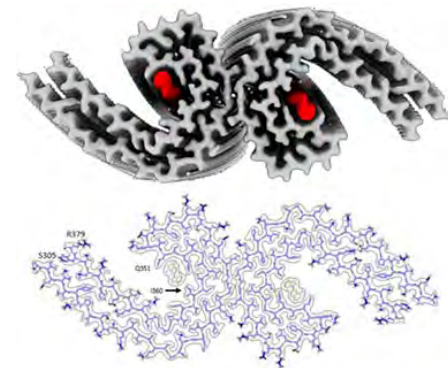
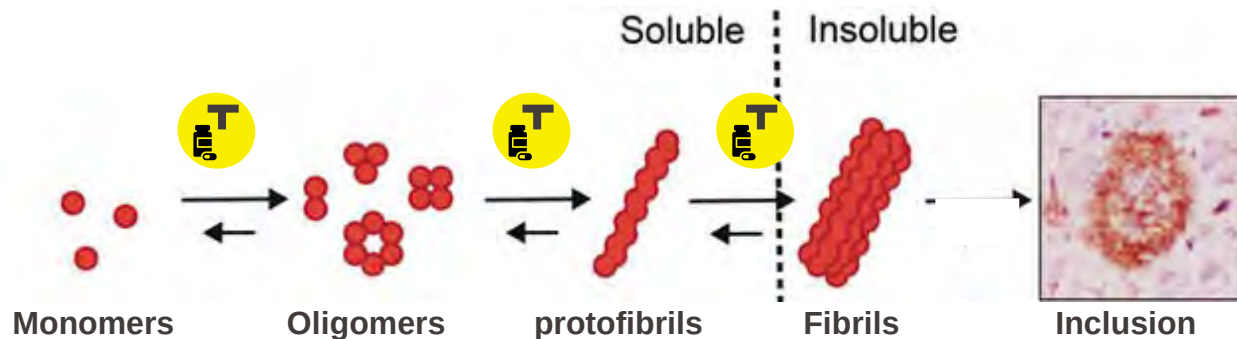


Guerrero-Ferreira R et al., 2018, eLife.

Before going to cellular models, we need first to understand the basic questions:

- a) What is the aggregation process ?
- c) What is the kinetics of aggregation ?
- d) What are the biophysics properties of the different species?
- e) Use Bioinformatics to find potential drugs/compounds that prevent aggregation or disassemble fibrils?

In vitro studies to understand the origin of the NDDs



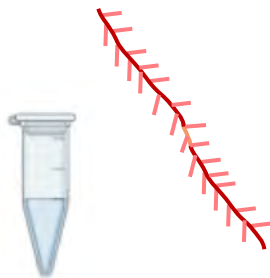
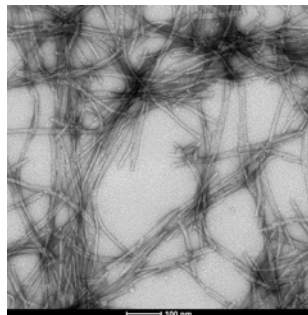
Tau CryoEM structures - AD

Before going to cellular models, we need first to understand the basic questions:

- a) What is the aggregation process ?
- c) What is the kinetics of aggregation ?
- d) What are the biophysics properties of the different species?
- e) Use Bioinformatics to find potential drugs/compounds that prevent aggregation or disassemble fibrils?

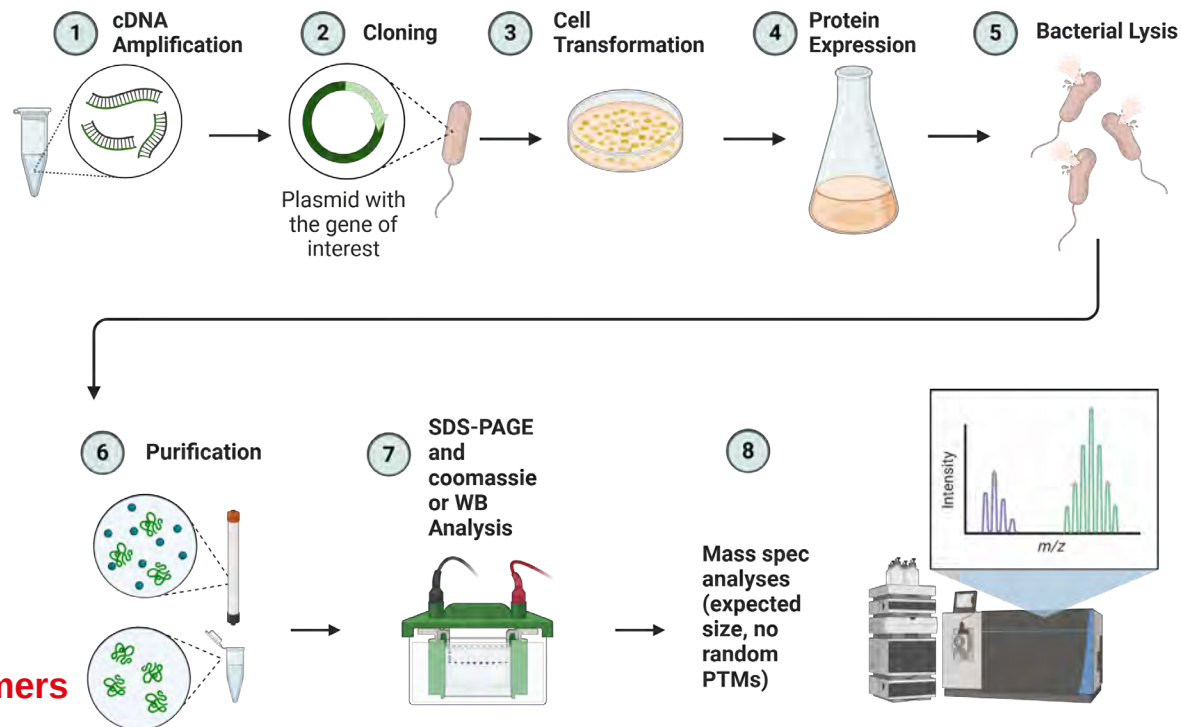
So how do we make each of these species in a test tube?

How to make fibrils and co ? **Step #1: production of prion-like proteins at the monomeric stage**

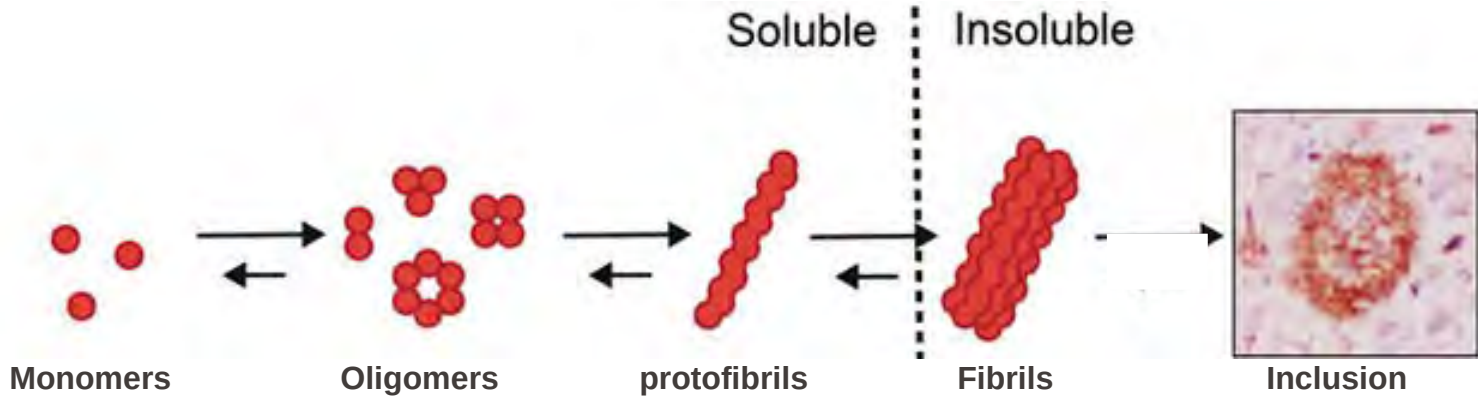


Recombinant
naked fibrils (in vitro)

Recombinant protein - cloning, expression and purification in *E.coli*



Monomers

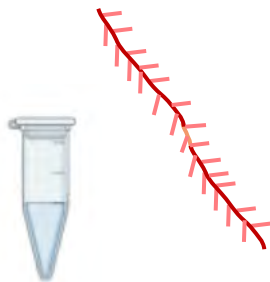
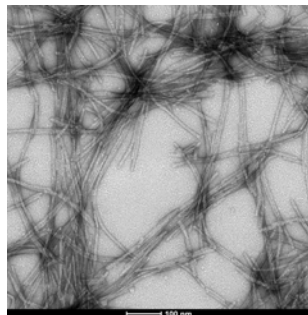


Adapted from [Elisabeth Nikitidou](#)



How to make fibrils and co ?

Step #2: aggregation of prion-like proteins – In vitro



Oligomers

Fibrils

Recombinant
naked fibrils (in vitro)

Aggregation prion-like proteins - In vitro

1 Dilute
protein in
PBS, Ph 7.5

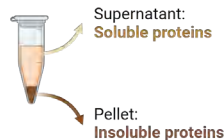
2 Shaking
5 days,
1'000 rpm,
37°C



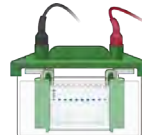
Oligomers
+ Fibrils

CHARACTERIZATION !!!!!!!

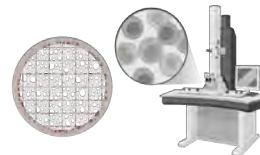
3 Solubility
Assay



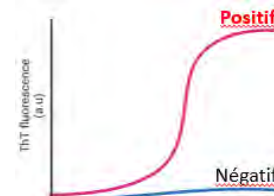
4 SDS-PAGE
WB or
coomassie
Analyses



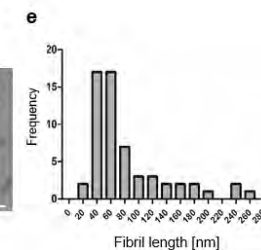
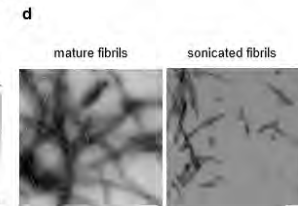
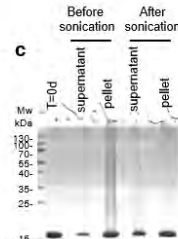
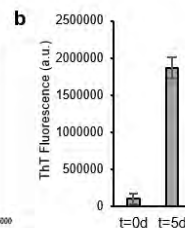
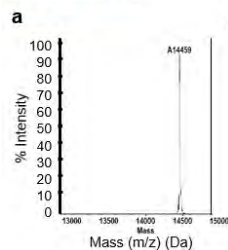
5 EM analyses

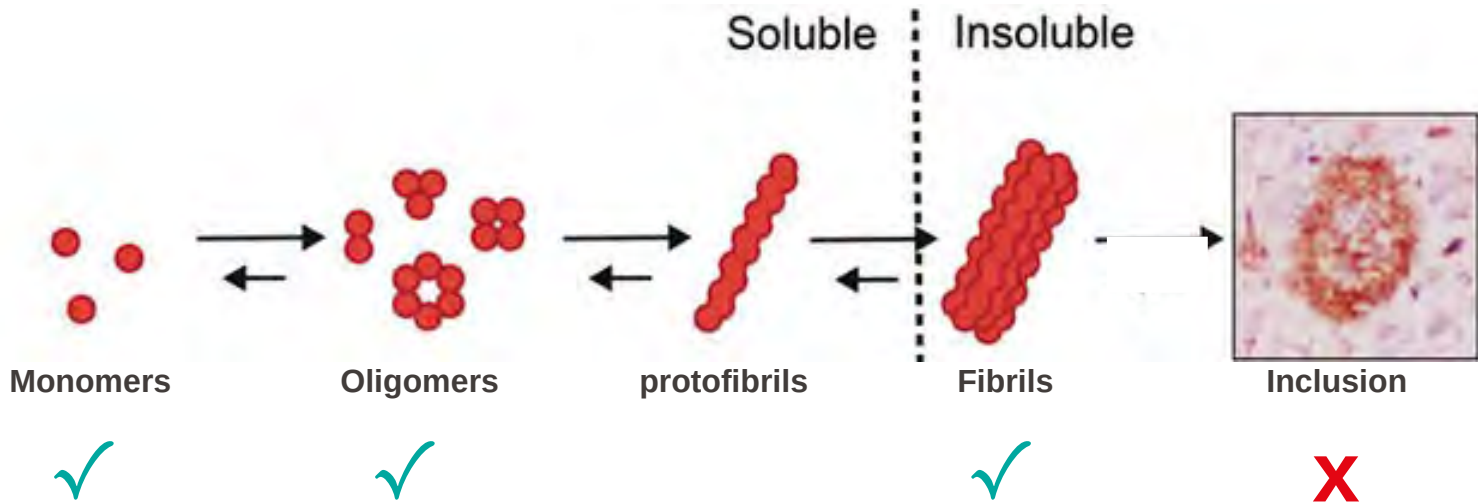


5 ThT aggregation



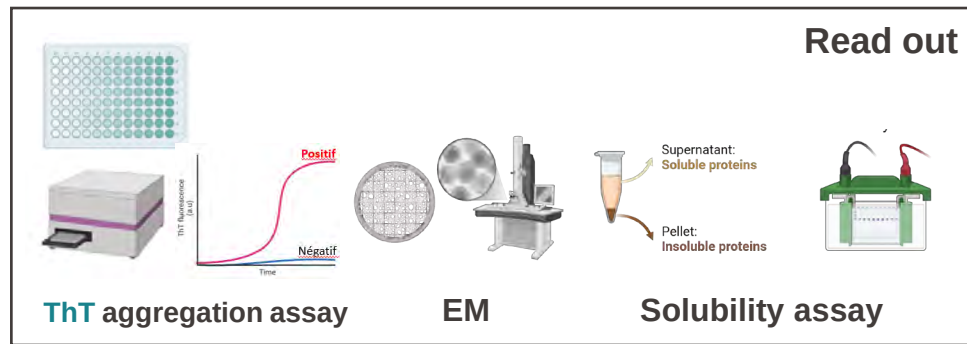
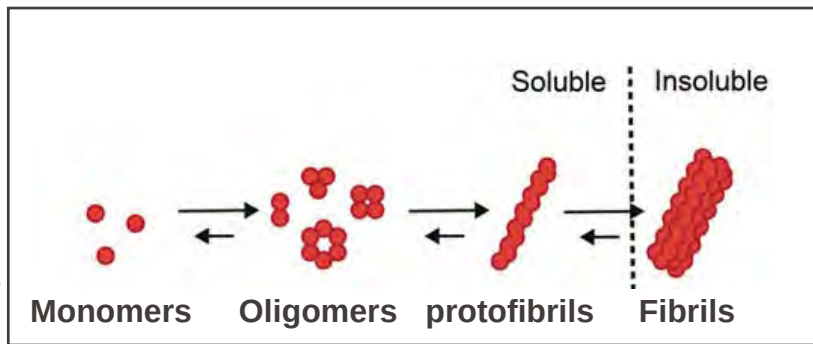
Human WT PFFs





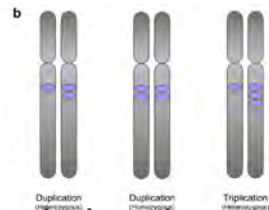
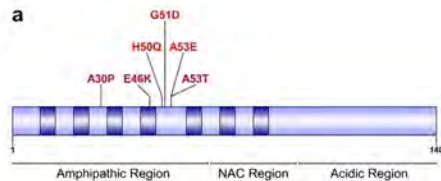
We can produce the different types of proteins from the soluble (physiological state) to the aggregates (pathological states) in vitro

OK but what can we do with these proteins at the bench side?

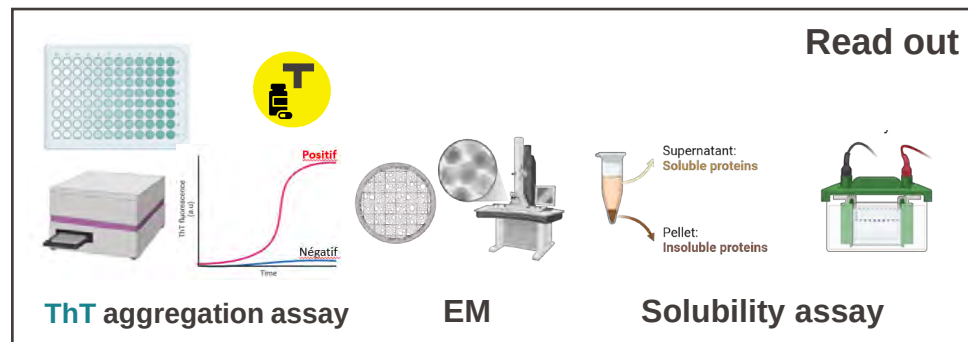
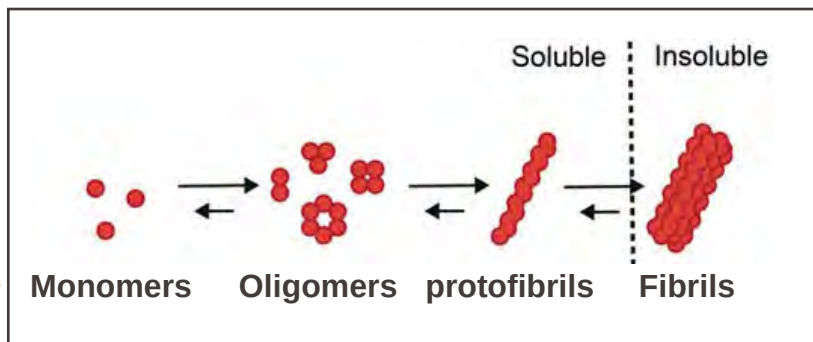


At the bench side:

- Understand how disease-associated mutations influence aggregation of WT proteins



- What can trigger protein aggregation (toxic insults: pesticides, lipids, other proteins, Ph, temperature.....)
- Follow the type of aggregates formed (oligomers, fibrils.....), their biophysics properties and structures (EM, CryoEM, NMR, AFM.....)
- Advantage: fast (<48h), cheap (<10\$/plate), high-throughput screening (386 well plates)

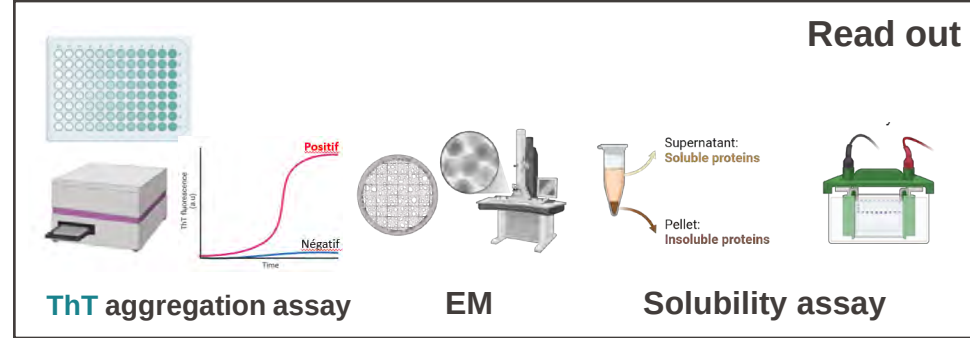
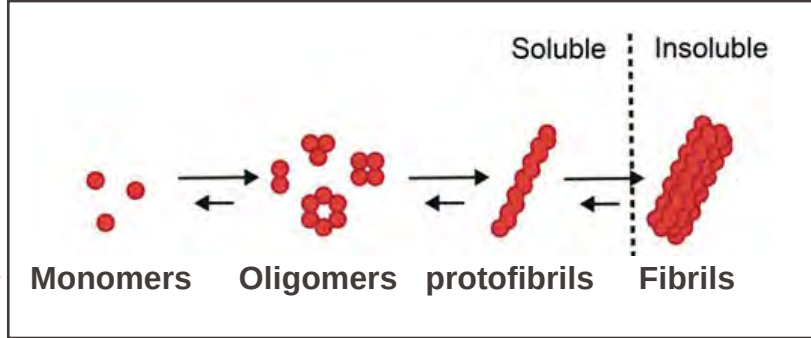


At the Drug discovery/screening side:

- Test library of:
 - chemical compounds
 - antibodies
 - venoms



- Advantage: fast (<48h), cheap (<10\$/plate), high-throughput screening (386 well plates)
- Disadvantage: Far from the complexity of an organism or even a neuron

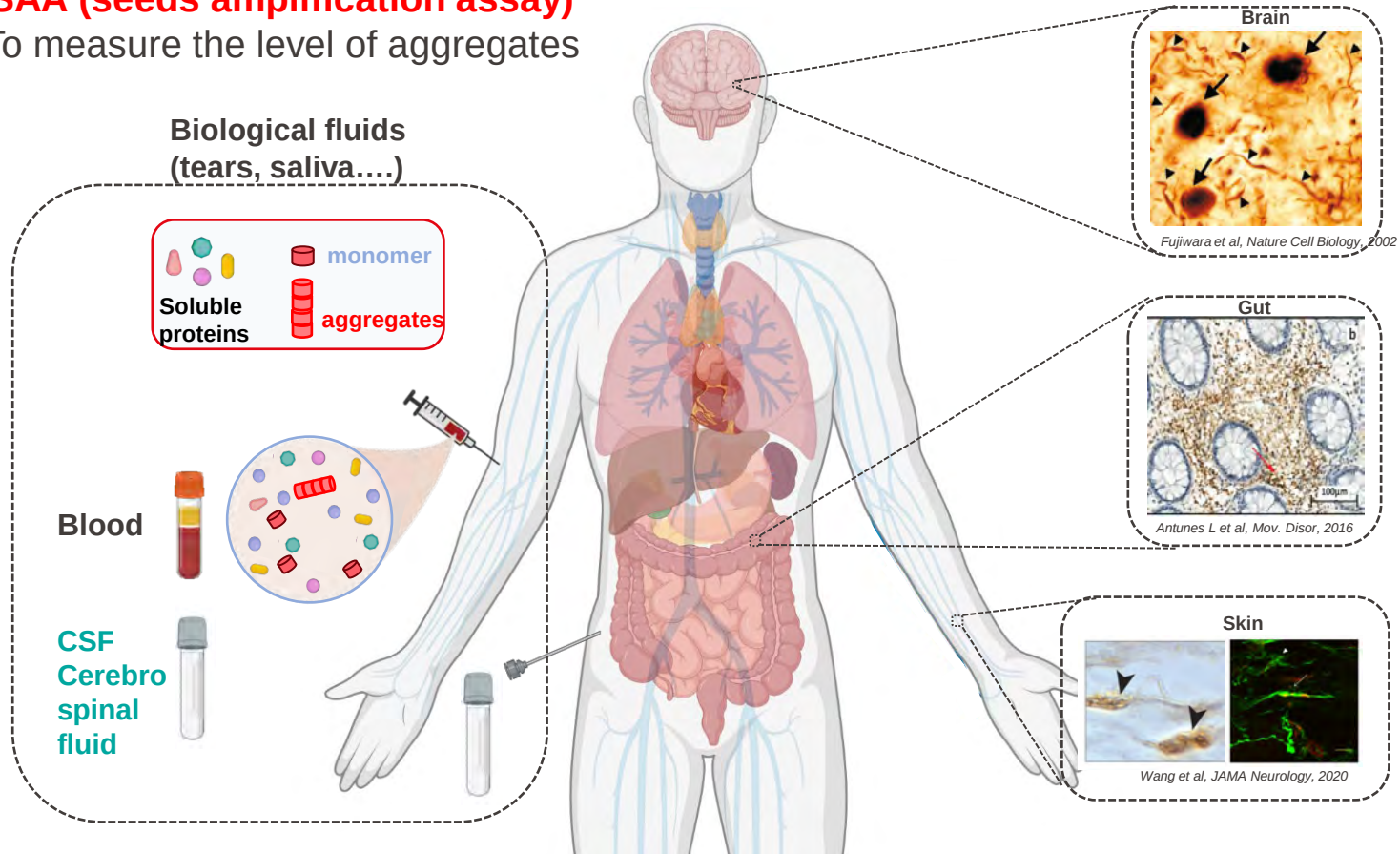


At the Biomarker side: New test for early diagnosis - 2023

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

SAA (seeds amplification assay)

To measure the level of aggregates



CSF
Cerebro
spinal
fluid



Can we detect **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

CSF
Cerebro
spinal
fluid

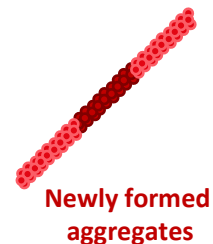
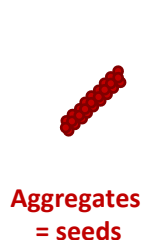


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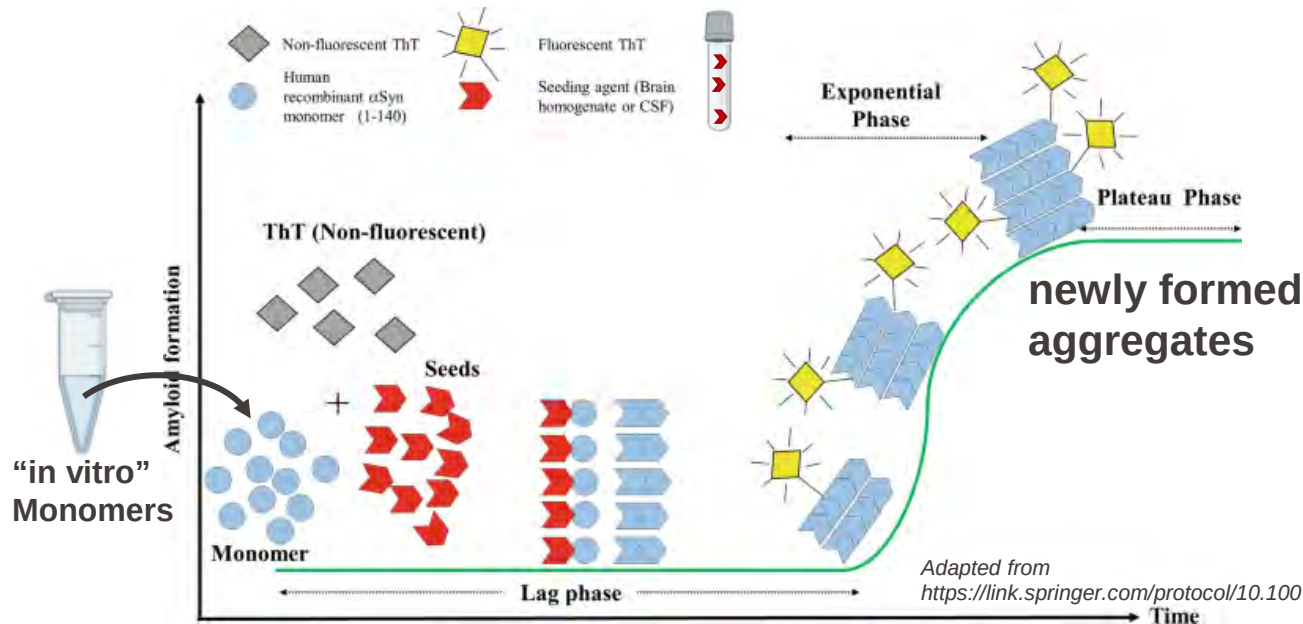


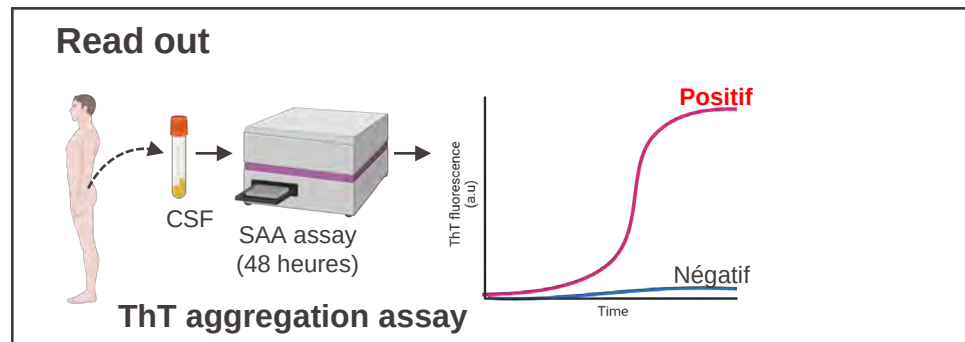
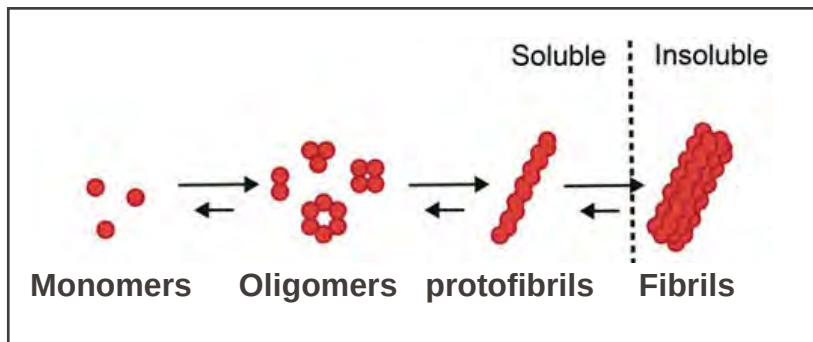
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Monomers + Seeds = newly formed aggregates





At the Biomarker side: New test for early diagnosis – clinical phases 2023

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)

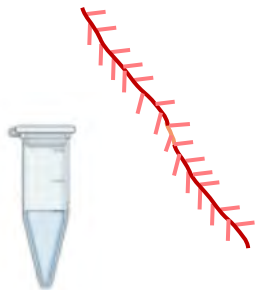
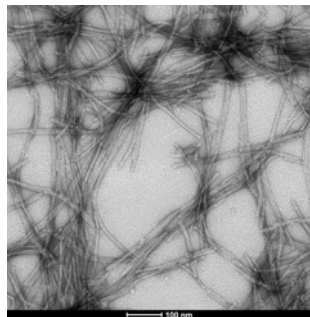


Parkinson's
Progression
Markers
Initiative

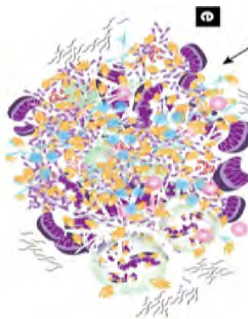
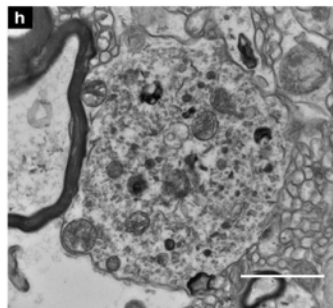
SAA has been acquired in 2428 PPmi participants <https://www.ppmi-info.org/>

- Advantage: fast (<48h), cheap (<10\$/plate), high-throughput screening (386 well plates)
- Disadvantage: false positive level

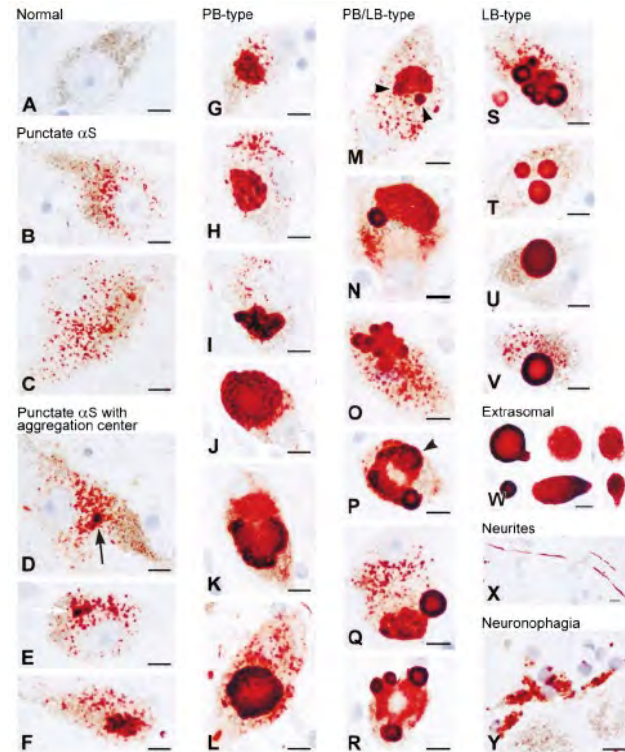
EPFL Challenges: ²⁶ A growing gap between the complexity of brain pathology and simplicity of cell-free systems? ★



Recombinant
naked fibrils (in vitro)



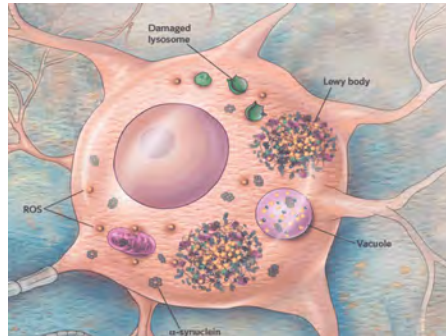
aSyn aggregates/inclusion
in PD brains



Shahmoradian S et al.,
Nat. Neuroscience, 2019

EPFL To what extent can we model the human PD pathology in cellular and animal models?

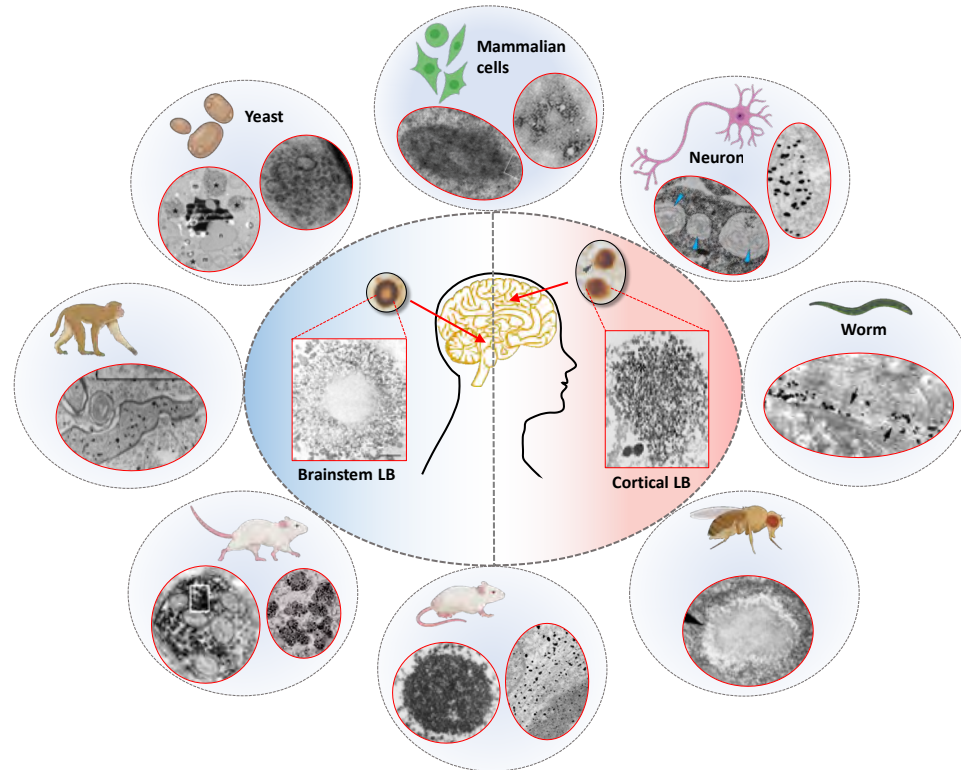
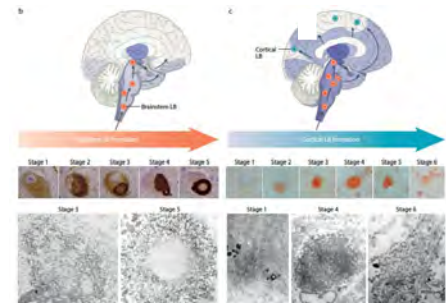
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nature
REVIEWS NEUROSCIENCE

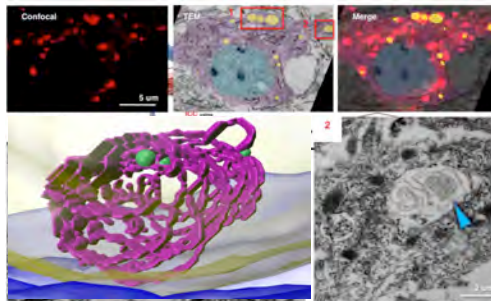
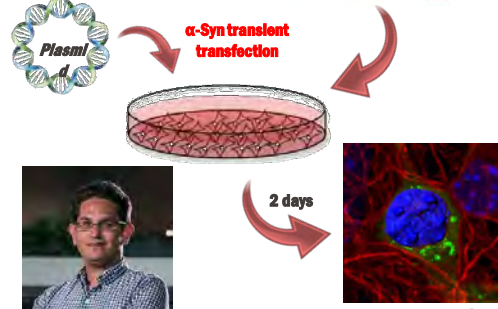
Reverse engineering Lewy bodies:
how far have we come and how far
can we go?

Mohamed Bilal Fares^{1,2,3}, Somanath Jagannath^{1,2} and Hilar A. Lashuel^{1,2,3}



Till recently, the existing cellular and animal models do not recapitulate the biochemical and ultrastructural properties of LBs

The aSyn overexpression-based models induces aSyn fibrillization but not LB formation

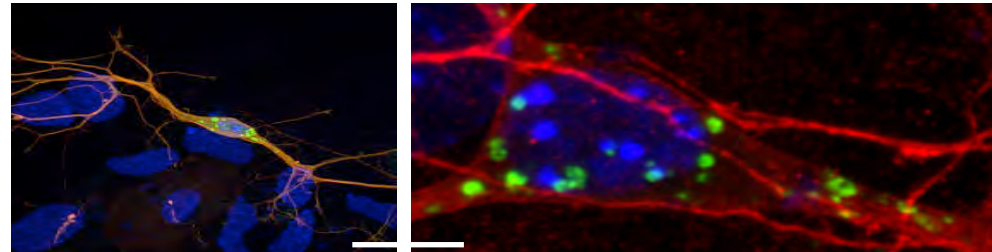
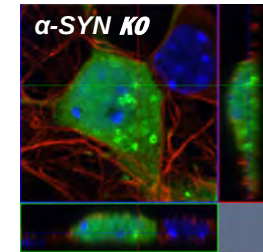
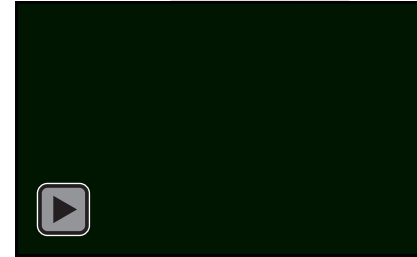
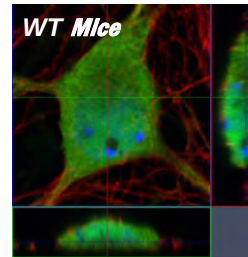


Induction of de novo α -synuclein fibrillization in a neuronal model for Parkinson's disease

Mohamed-Bilal Fares^a, Bohumil Maco^a, Abid Oueslati^{a,1}, Edward Rockenstein^b, Natalia Ninkina^c, Vladimir L. Buchman^c, Eliezer Masliah^b, and Hilal A. Lashuel^{a,4,2}

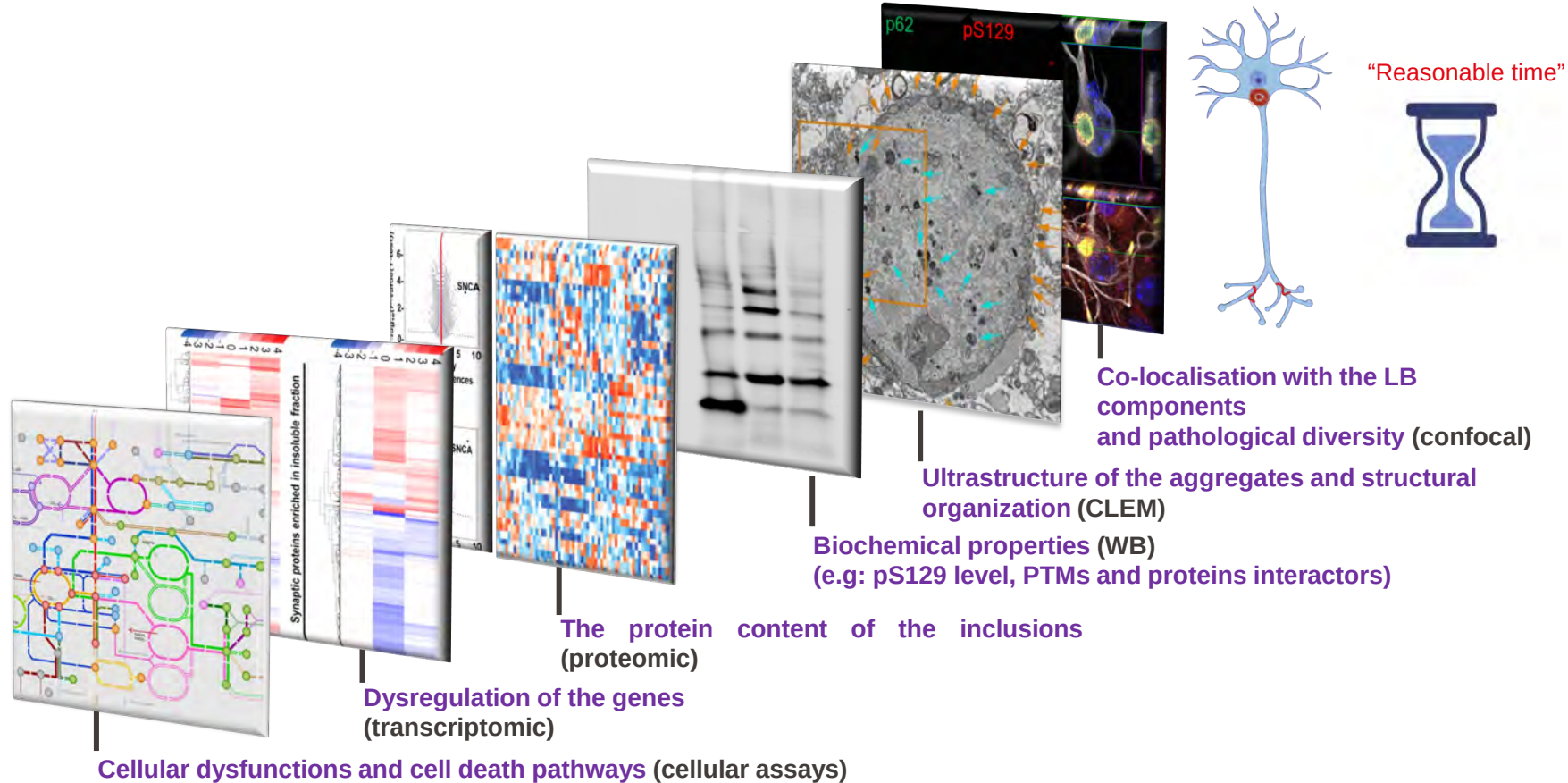
^aBrain Mind Institute, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, CH-1015, Switzerland; ^bDepartment of Neurosciences, University of California San Diego, La Jolla, CA 92093; ^cSchool of Biosciences, Cardiff University, Cardiff, CF10 3AX, United Kingdom; and ⁴Qatar Biomedical Research Institute, Hamad Bin Khalifa University, Doha, 5825, Qatar

Edited by Thomas C. Südhof, Stanford University School of Medicine, Stanford, CA, and approved January 4, 2016 (received for review July 25, 2015)



aSyn overexpression in aSyn KO neurons induces aSyn fibrillization, but not LB formation

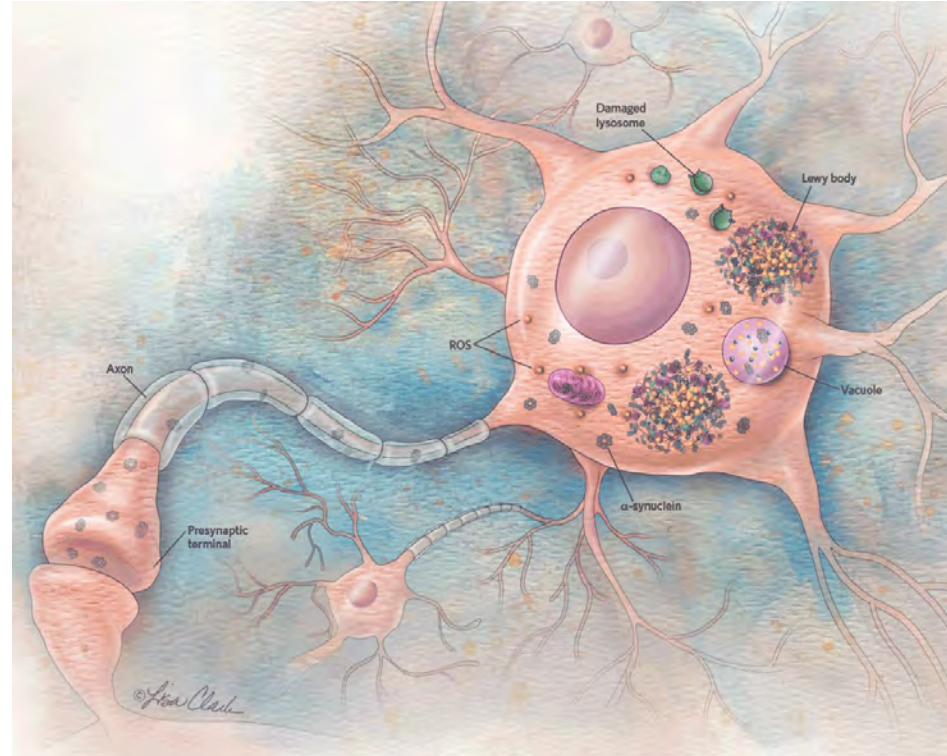
Which features of the human pathology should the ★ Cellular and animal models reproduce?



LashuelLab



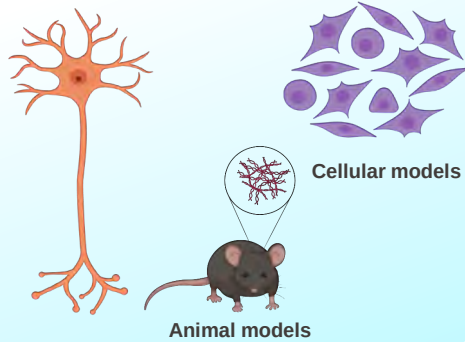
Inspired by patients.
Driven by science.



© Lisa Clark. The Scientist :<https://www.the-scientist.com/features/is-it-time-to-rethink-parkinsons-pathology-66449>

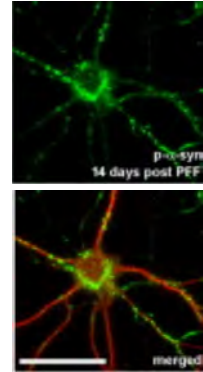
EPFL Models of aSyn pathology formation and propagation in the absence of aSyn overexpression

Disease-Relevant Models

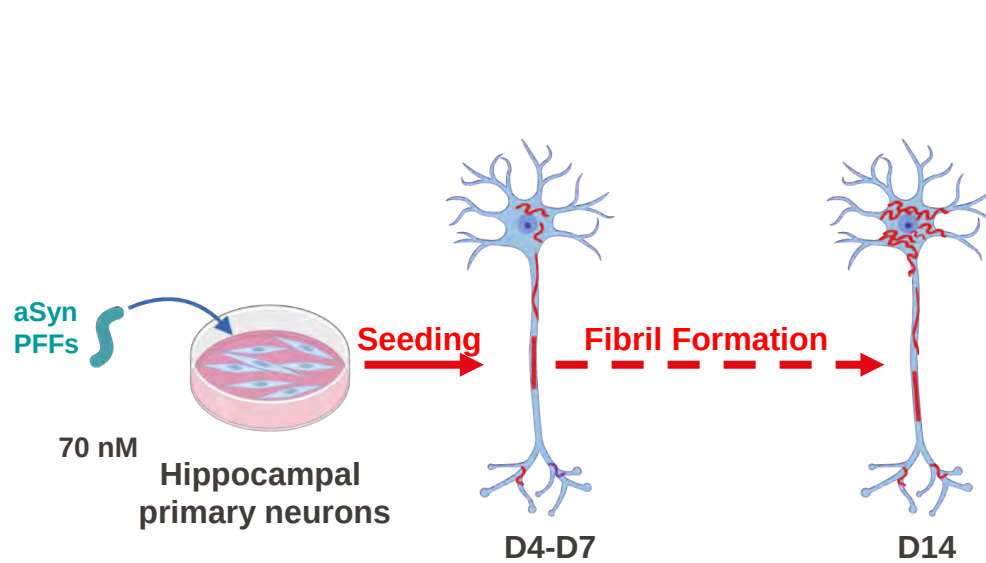


Addition of exogenous α -synuclein preformed fibrils to primary neuronal cultures to seed recruitment of endogenous α -synuclein to Lewy body and Lewy neurite-like aggregates

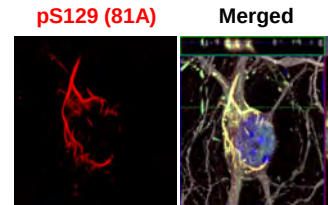
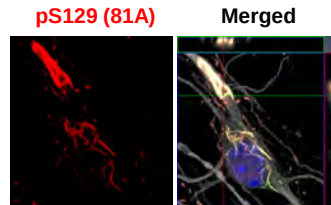
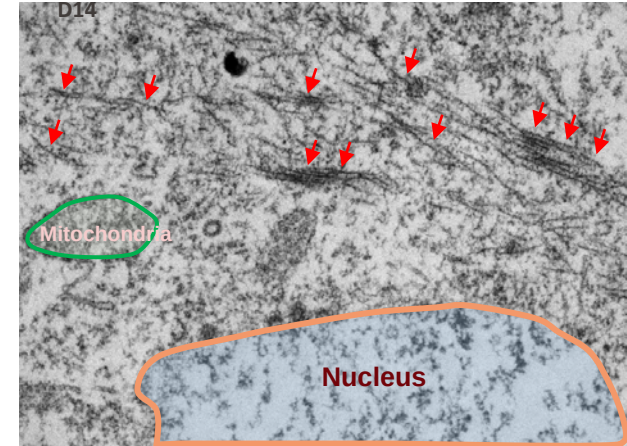
Laura A Volpicelli-Daley¹, Kelvin C Luk² & Virginia M-Y Lee² **NATURE PROTOCOLS** | VOL.9 NO.9 | 2014 | 2135



EPFL The extended version of the neuronal seeding model allows the formation and maturation of LB-like inclusions



aSyn newly formed fibrils in PFF-treated neurons –

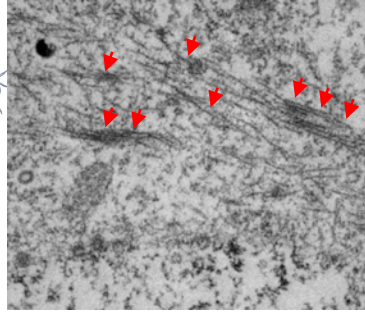
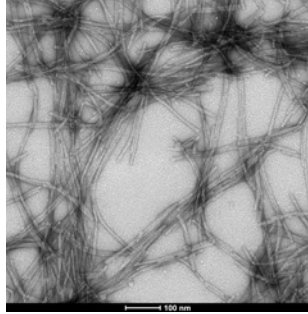


EPFL Can we bridge the gap between the complexity of brain pathology and simplicity of cell-free systems?

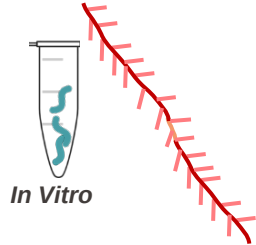
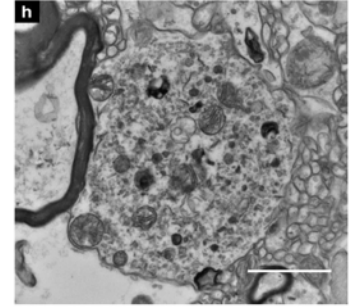


LashuelLab

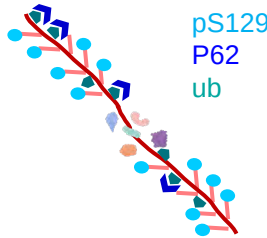
Bona fide LB from human tissues



?



In Vitro



Recombinant
naked fibrils

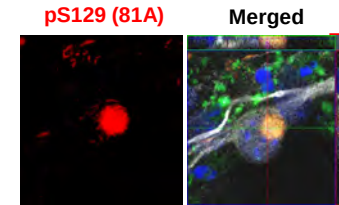
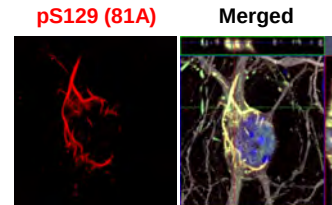
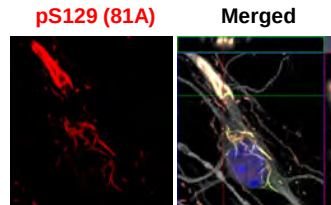
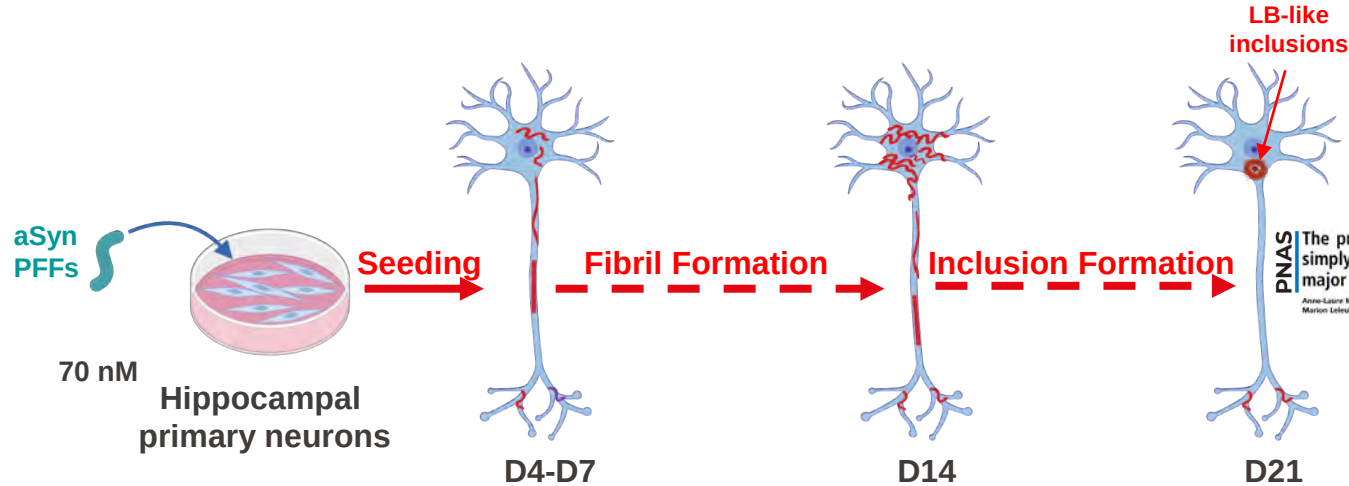
Neuron-derived Fibrils
Site-specific PTMs of fibrils



What do aSyn aggregates
look like in PD brains?

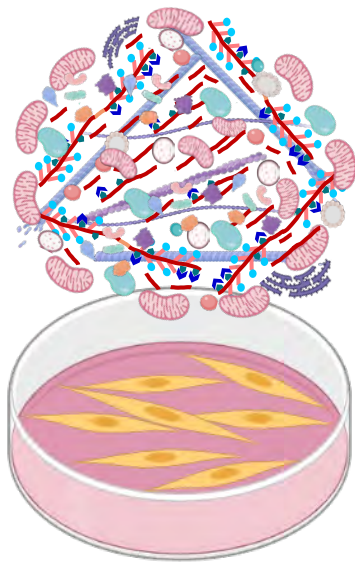
Shahmoradian S et al., Nat.
Neuroscience, 2019

EPFL The extended version of the neuronal seeding model allows the formation and maturation of LB-like inclusions

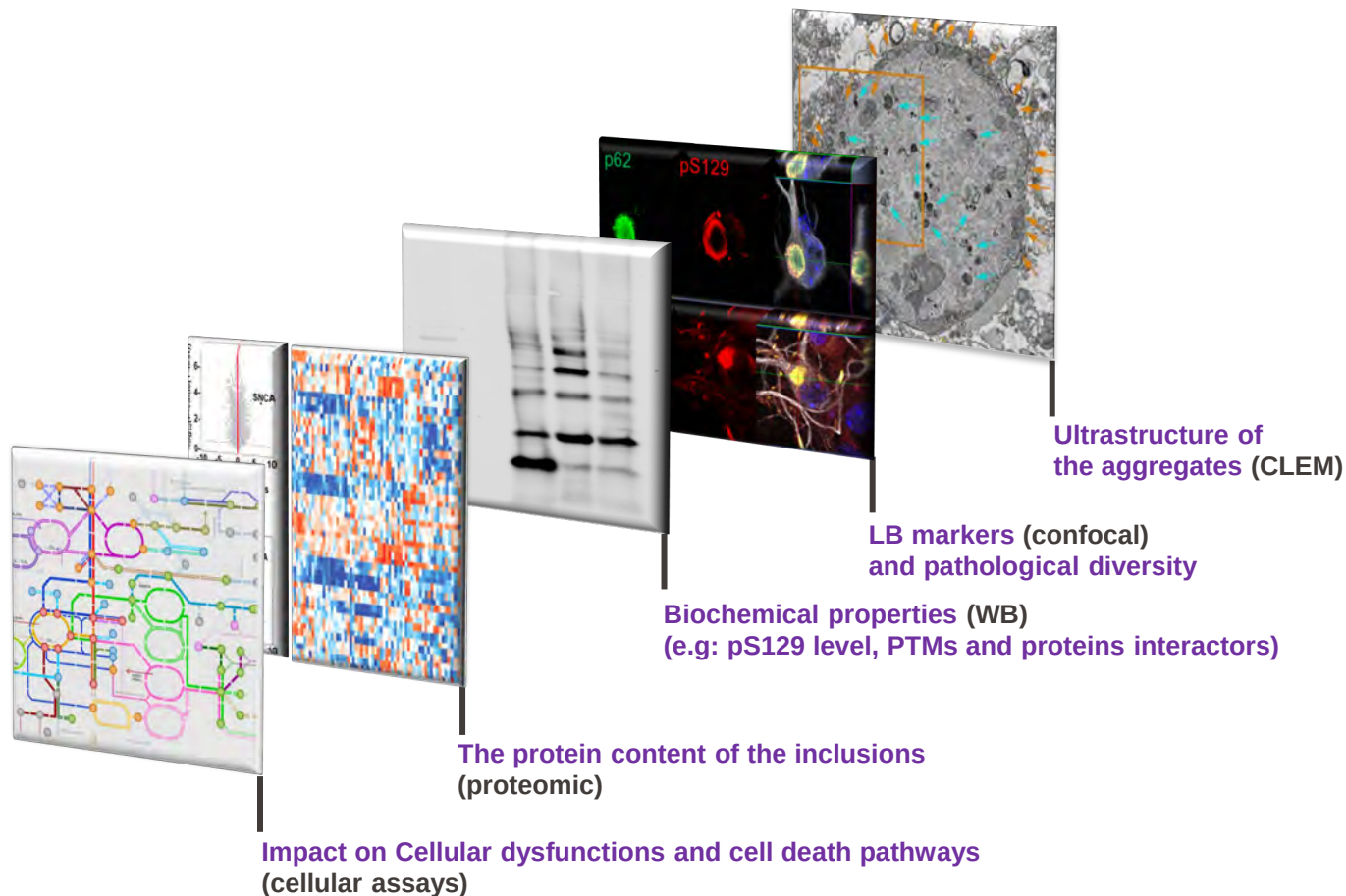


PNAS The process of Lewy body formation, rather than simply α -synuclein fibrillization, is one of the major drivers of neurodegeneration

Anne-Laure Mahul-Maier¹, Johannes Bartscher¹, Niran Maharjan¹, Laura Wessens¹, Marie Croisier¹, Fabien Kuttler¹, Marion Lelou¹, Graham W. Knott², and Hilal A. Lashuel^{1*}



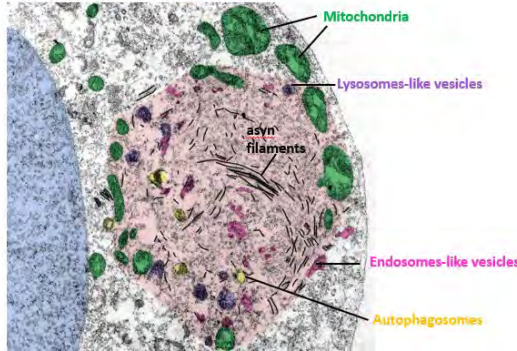
Lewy body in a dish



EPFL The neuronal Lewy body model enables the reproduction of inclusions similar to those found in patients

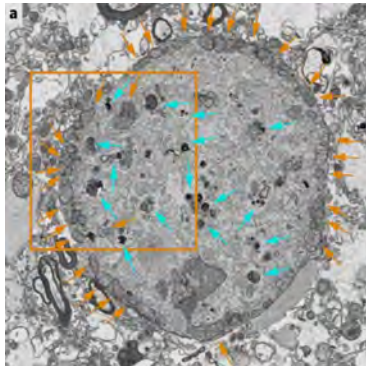
Ultrastructure

Lewy bodies in primary neurons



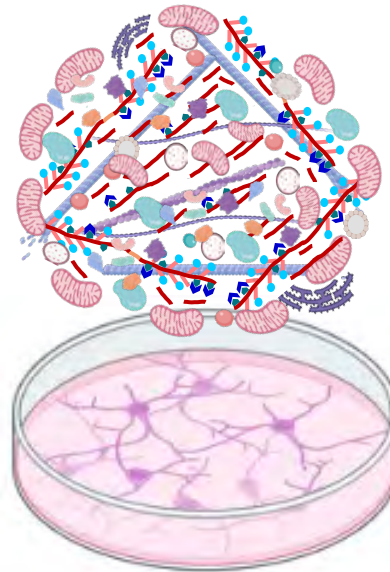
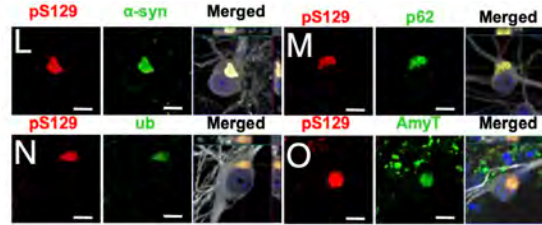
Mahul-Mellier et al., 2020, PNAS

Lewy body in patients



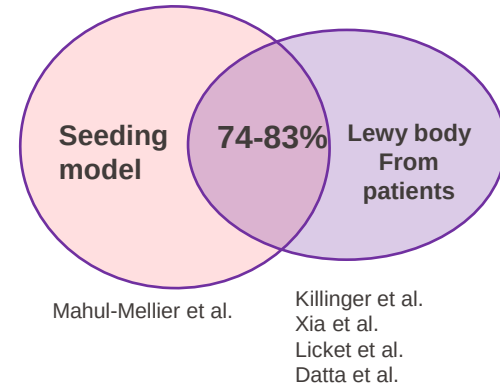
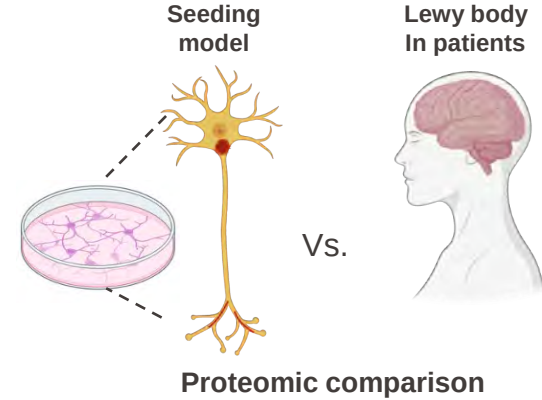
Shahmoradian et al., Nature Neurosciences, 2019

LBs markers

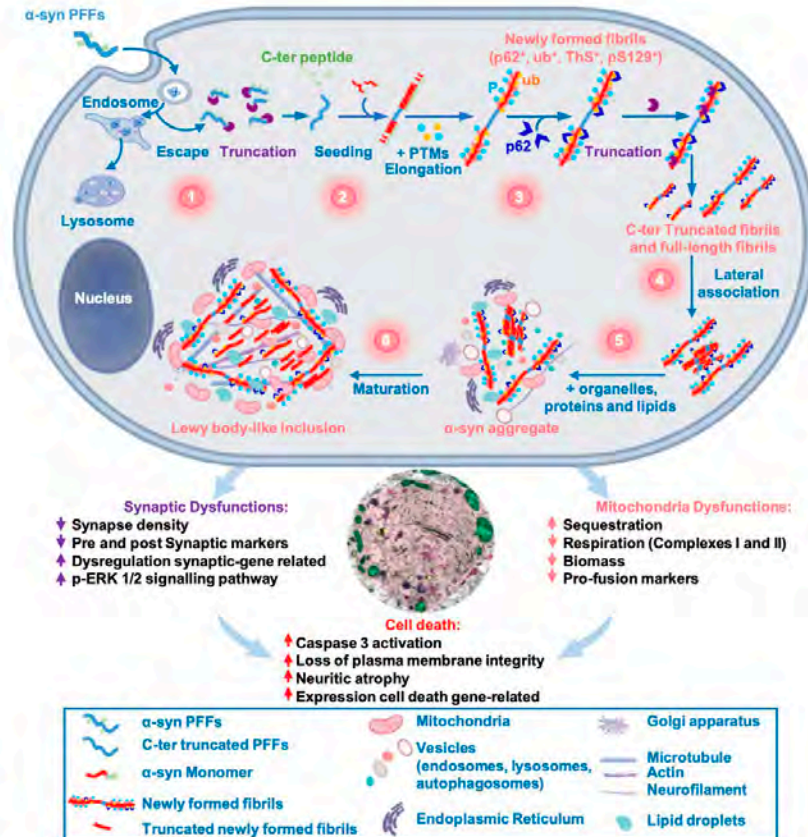


Lewy body in a dish

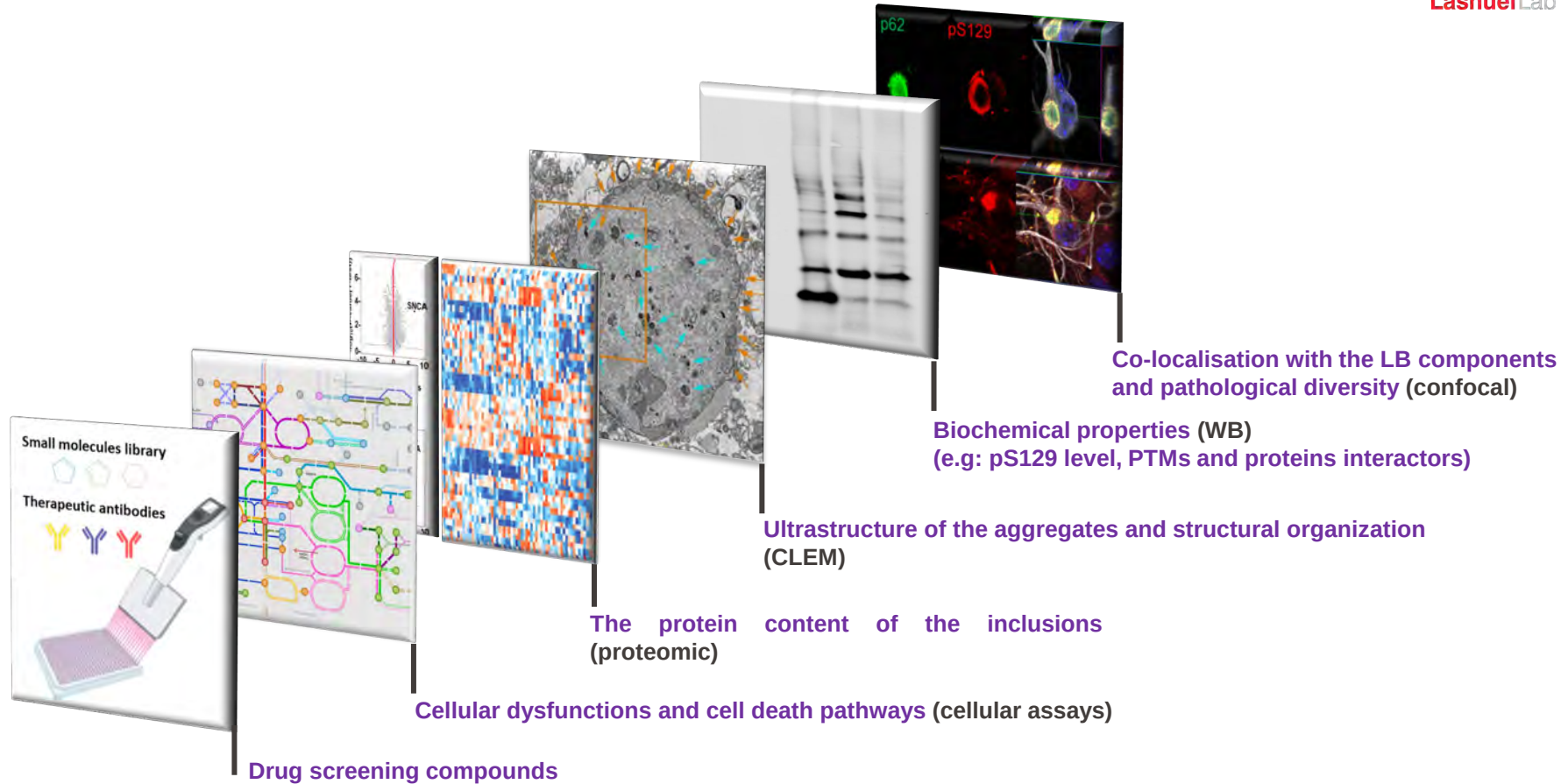
Proteomics



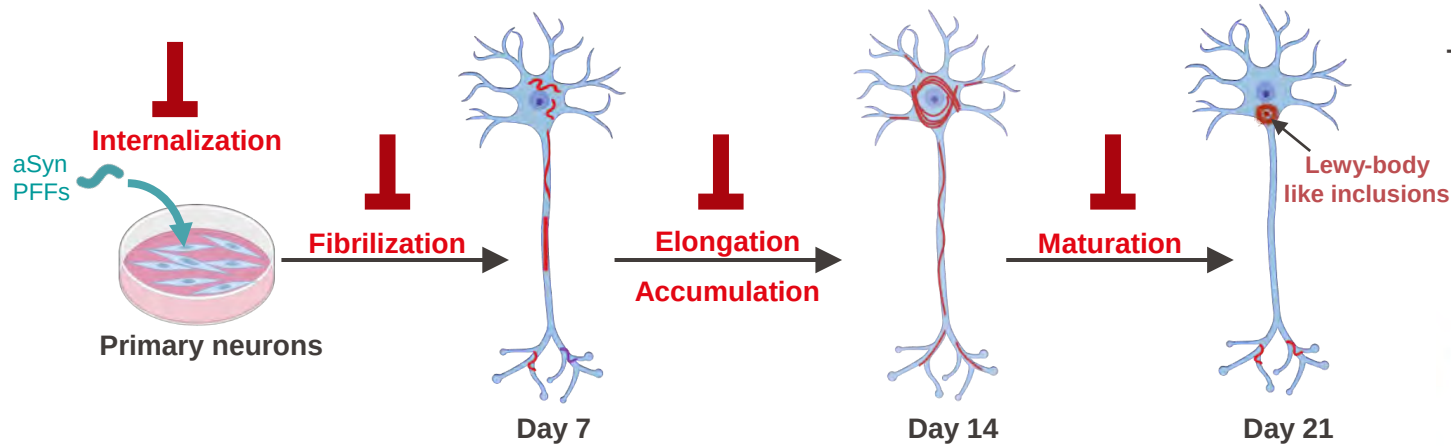
EPFL The Lewy body seeding model allows for the dissection of the mechanisms underlying Parkinson's disease



EPFL Application: a powerful platform for drug screening



EPFL Application: a powerful platform for drug screening



Small molecules library



Therapeutic antibodies

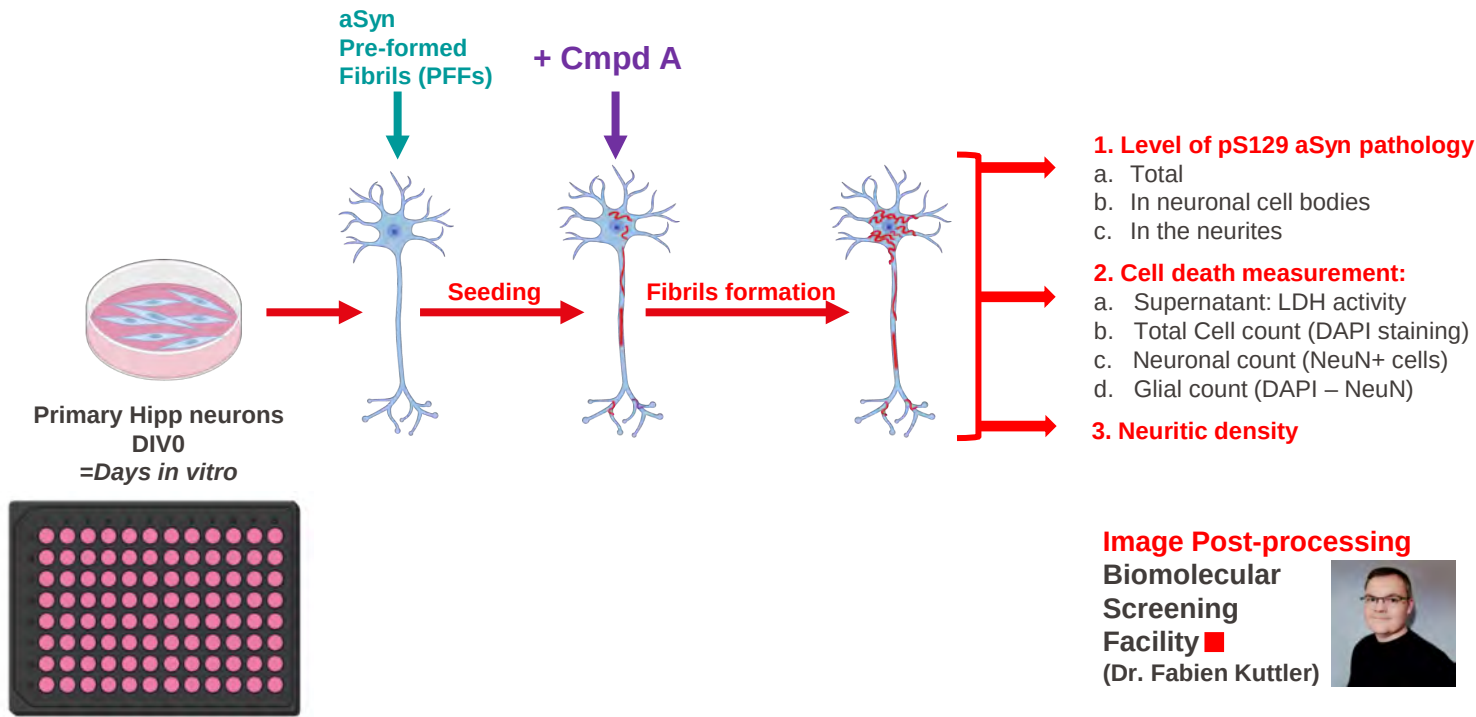


Venoms

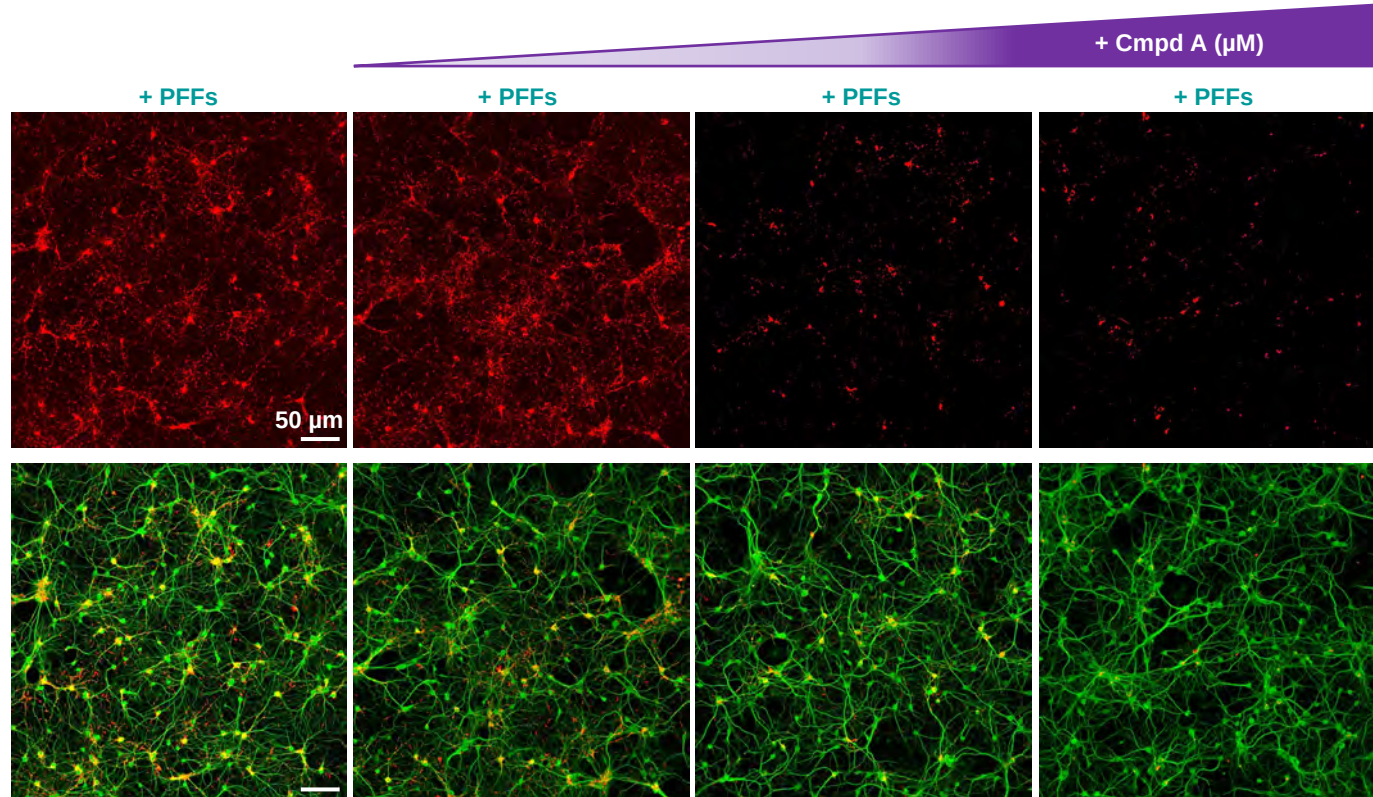


Can we slow down or reduce aSyn pathology ?

Automated high content screening image analysis pipeline for drug screening



EPFL The neuronal seeding model: a platform for drug screening



EPFL Application: a powerful platform for drug screening



■ Bio480 — How to model NDDs at the bench toward therapeutics discovery

Small molecules



Immunotherapy

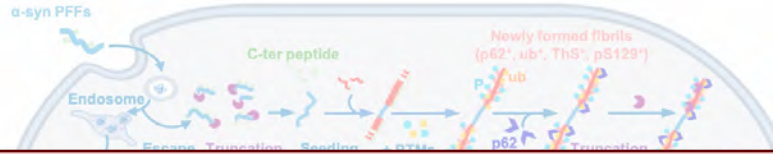


Venoms



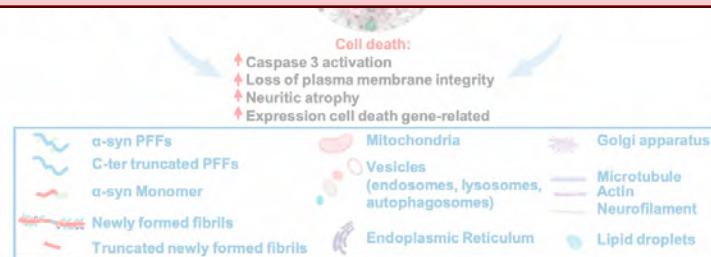
Can we slow down or reduce aSyn pathology ?

EPFL The Lewy body seeding model allows for the dissection of the mechanisms underlying Parkinson's disease



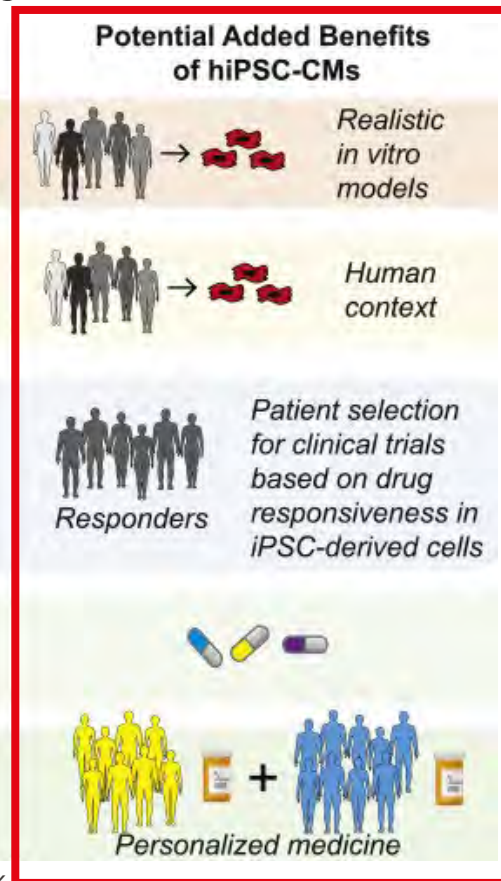
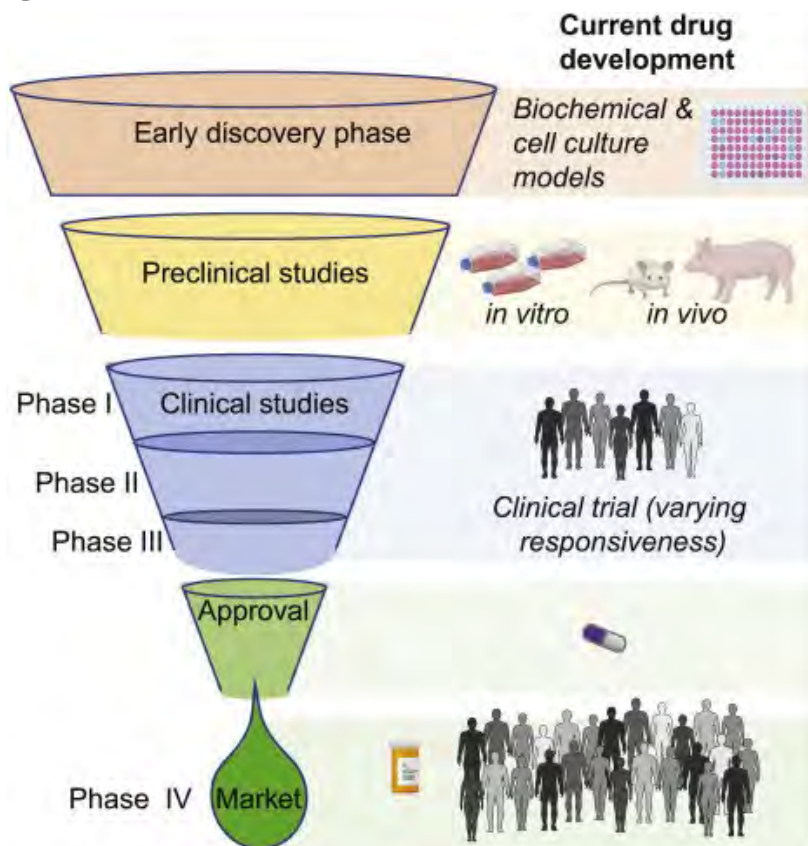
Limitations of the model:

- 1 Mouse aSyn $\neq$ Human aSyn
- 2 Does not recapitulate the full biochemical and morphological diversity of PD pathology
- 3 Short-timeline: Not suitable to study late stages of LB formation or LB Clearance



Bench to Bedside: ★

Translating Science from the lab to the Clinic



<https://www.sciencedirect.com/science/article/pii/S245194562100101X>

Lewy Body in a dish:

Translating the seeding model in human iDA



Dr. Anne-Laure
Mahul-Mellier



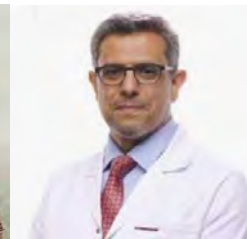
Lukas
Van den Heuvel



Manel
Boussouf



Yllza
Jasiqi



Prof. Hilal A.
Lashuel



Dr. Razan
Sheta

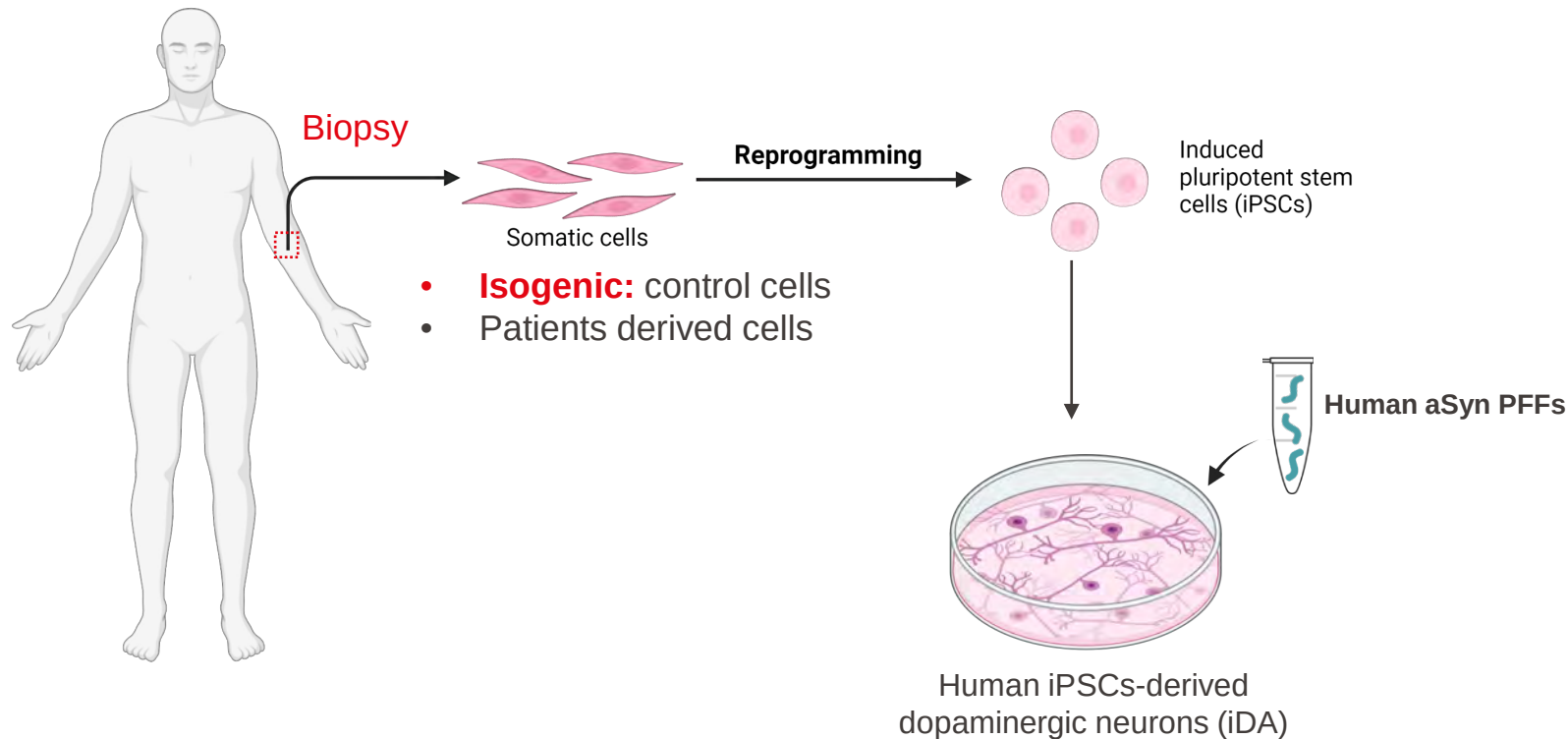


Maxime
Teixeira



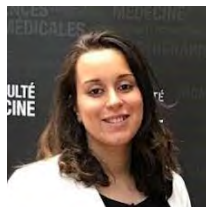
Prof. Abid
Oueslati

Lewy Body in a dish: Translating the seeding model in human iDA



Current iPSC-based models of PD have limitations:

- 1) They fail to reproduce LB pathology in both neurites and cell bodies within a reasonable time
- 2) They require the artificial overexpression of aSyn to achieve any pathology.



Dr. Razan Sheta



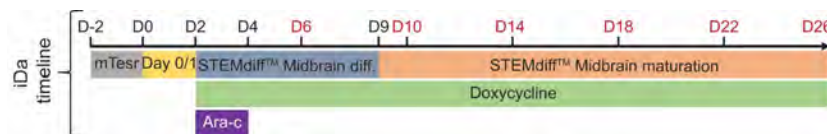
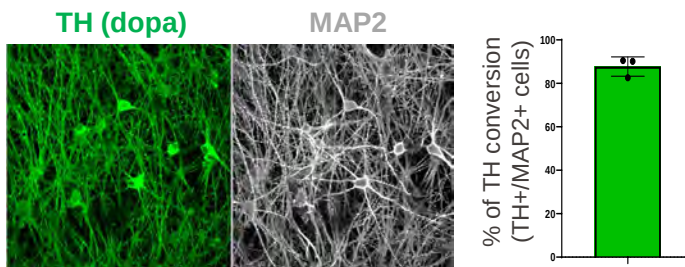
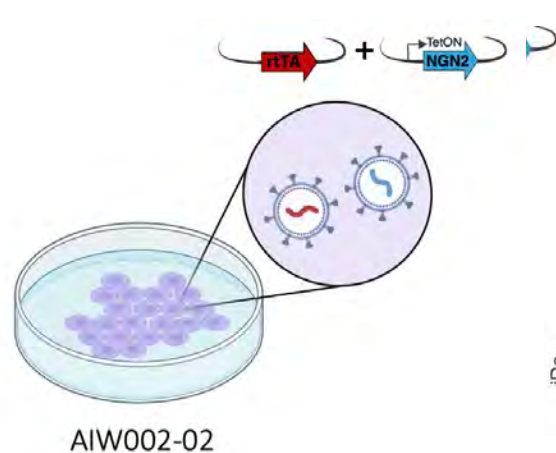
Maxime Teixeira



Prof. Abid Oueslati

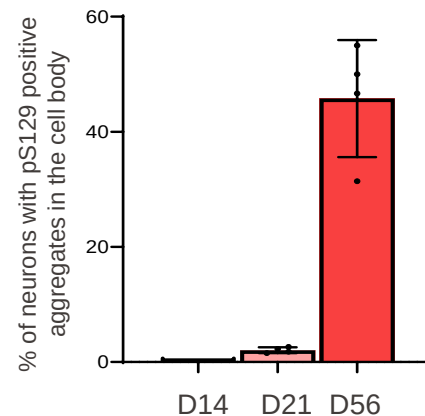
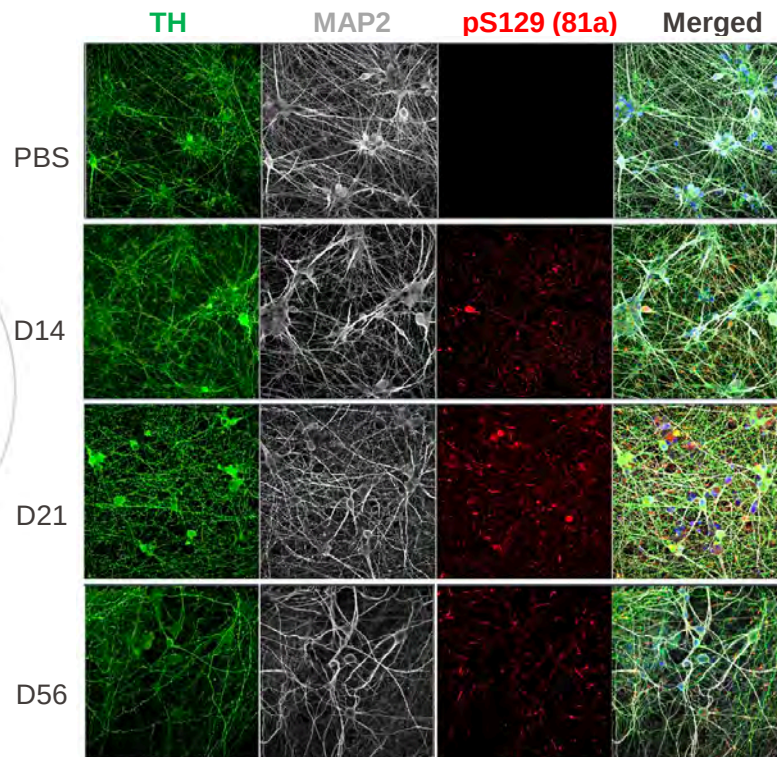
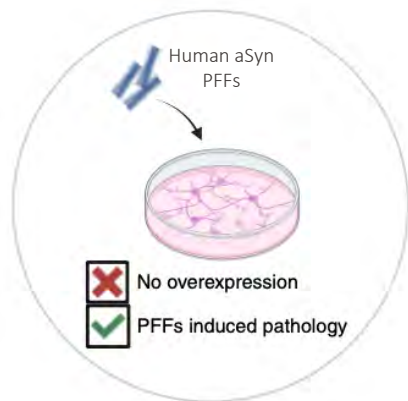
Combining NGN2 programming and dopaminergic patterning for a rapid and efficient generation of hiPSC-derived midbrain neurons

Razan Sheta^{1,2,11}, Maxime Teixeira^{1,2,11}, Walid Idj^{1,2,11}, Marion Pierre³, Aurelie de Rus Jacquet^{1,4}, Vincent Emond¹, Cornelia E. Zorca^{5,6}, Benoît Vanderperre^{7,8}, Thomas M. Durcan^{5,6}, Edward A. Fon^{5,6}, Frédéric Calon^{1,9}, Mohamed Chahine^{3,10} & Abid Oueslati^{1,2,11}



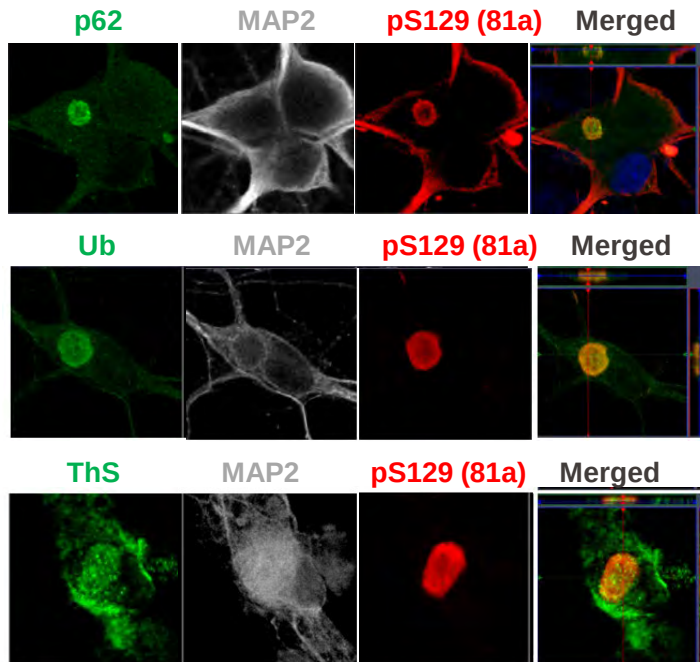
~80 % of the iNeurons convert in iDopaminergic neurons (iDa)

EPFL Seeded iDAs form neuritic and somatic pS129 pathology

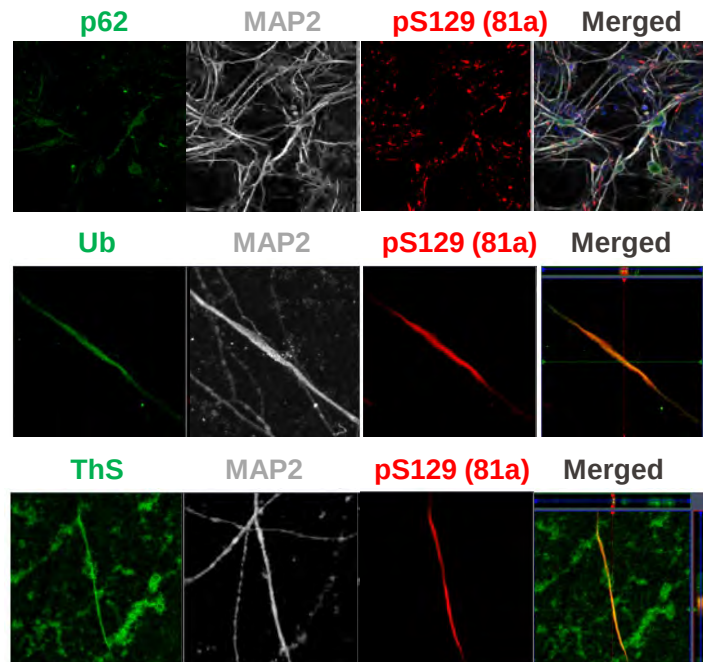


- Formation of aSyn-pS129 pathology first in neurites and then in cell bodies
- Percentage of aggregates formed in cell bodies increased overtime

Somatic inclusions



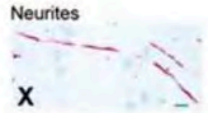
Neuritic inclusions



Bona fide LBs display sequestration of various pathological markers:

- **p62** (in cell bodies only, similar to what is observed in PD brains)
- **ubiquitin**
- **Amyloid-specific dyes (ThS)**

EPFL The iDA seeding model replicates
The morphological heterogeneity of human pathology in PD brains

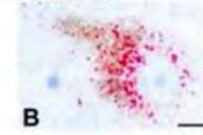


Kuusisto et al., 2003

Punctate α S



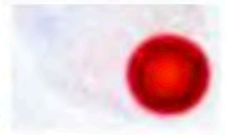
Punctate α S



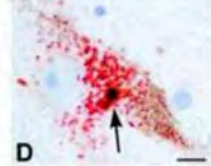
LB



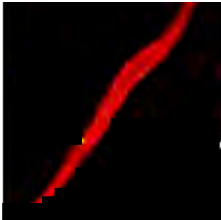
LB



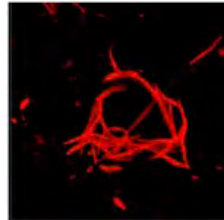
Punctate α S with aggregation center



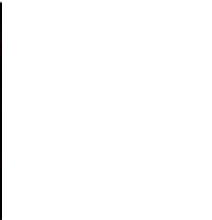
Neuritic aggregates



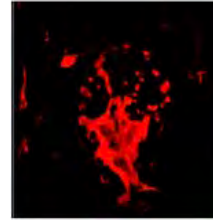
Filamentous-like
Like aggregates



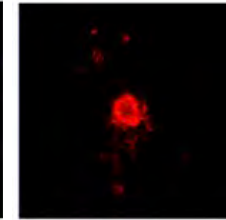
Super tiny-like
aggregates



Speckled-like
Aggregates
(granular and/or lines)



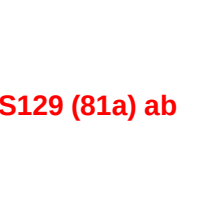
Ring-like LB



Dense-like LB

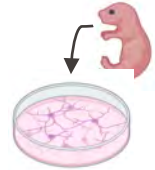


Speckled
Aggregates + LB

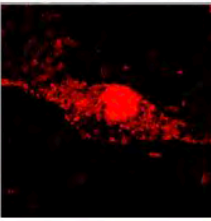
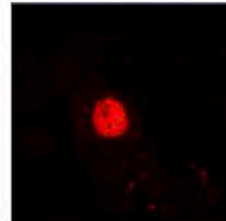
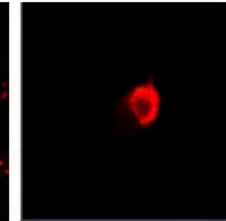
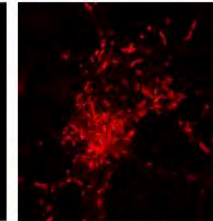
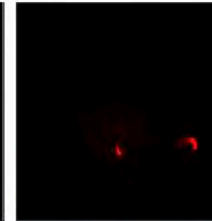
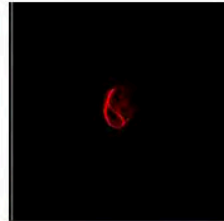
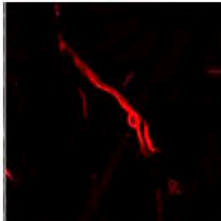
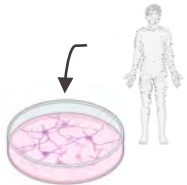


Detection with pS129 (81a) ab

Primary neurons

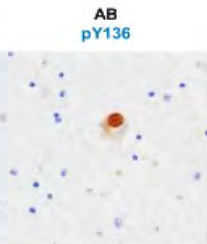
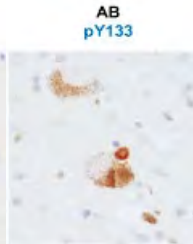
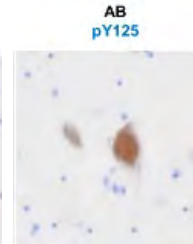
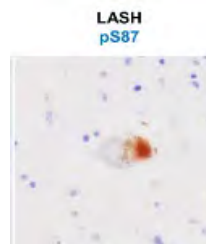


Seeded iDA

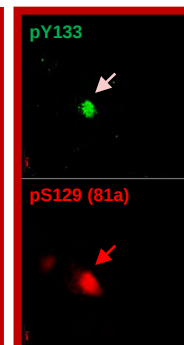
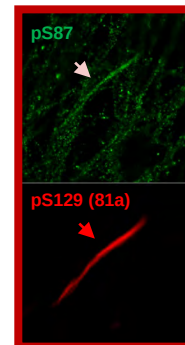
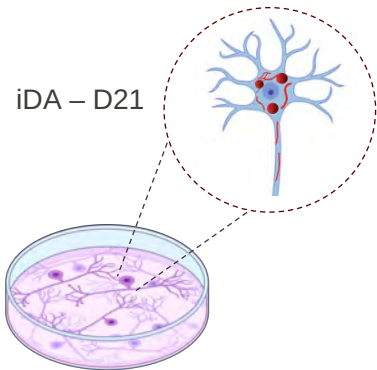


EPFL The iDA seeding model replicates The PTMs signature associated with the human pathology

Human Brain



iDA – D21



EPFL The iDA seeding model replicates The PTMs signature associated with the human pathology



Lashuel Lab



Lukas
Van den Heuvel



Dr. Graham Knott



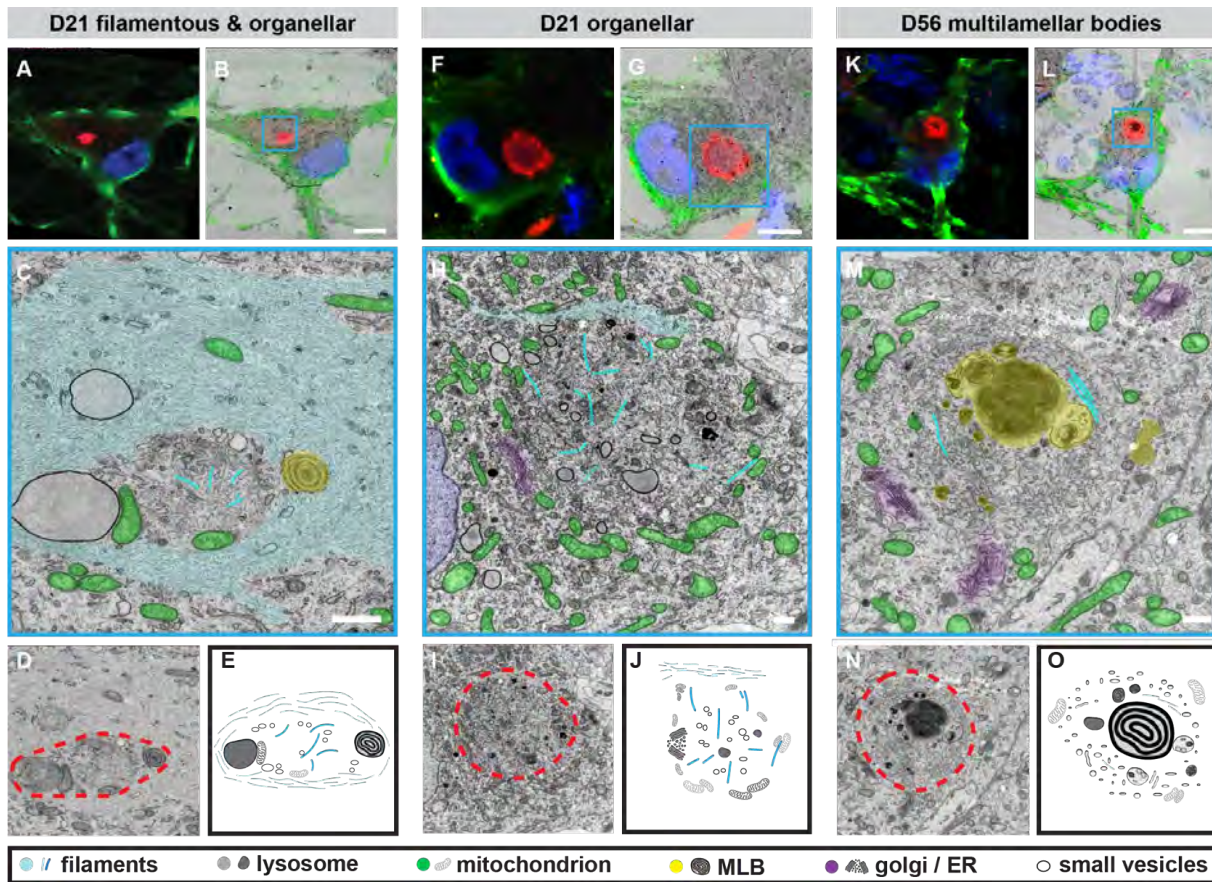
Mary Croisier



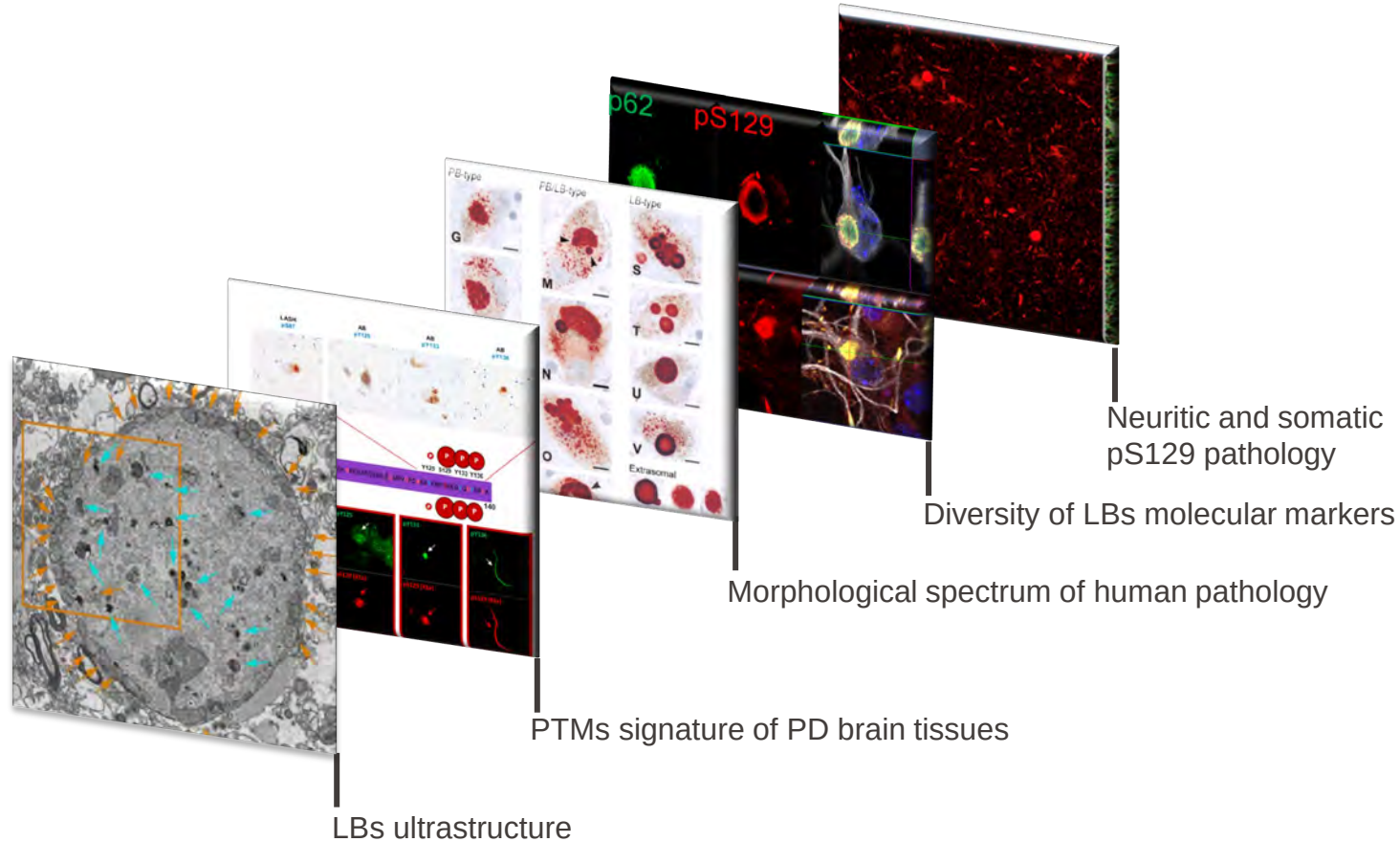
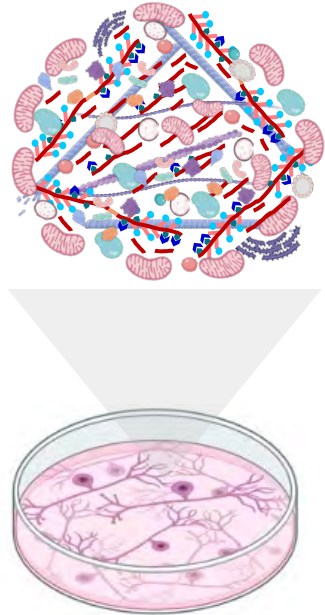
Stéphanie Rosset



Jérôme Blanc
BioEM lab EPFL



Lewy body in a dish

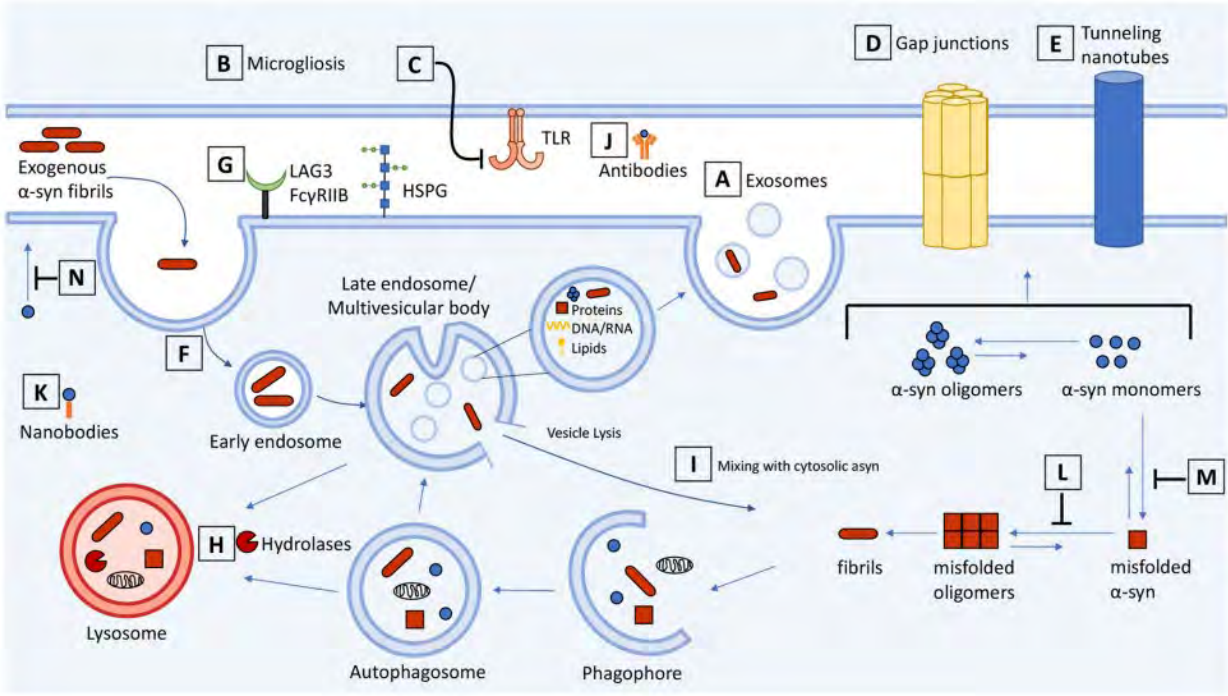


Why is it so important to solve the cellular mechanisms and signalling pathways behind the NDDs ?

Because they are druggable

- I. Modeling neurodegenerative disorders (NDDs) in the Lab
- II. Drugs therapy in Clinical trials**
- III. Bench techniques applied to early diagnosis

EPFL Cell-to-cell transmission, internalization, and trafficking of aSyn and therapeutic targets along the pathways



Menon et al., 2022

TABLE 1 | Therapeutic targets and drugs from Figure 1.

Target	Drugs
1) Inhibitors of microglial activation Figure 1B	Hypoestoxide Lenalidomide Candesartan cilexetil
2) Microglial toll-like receptor inhibitors Figure 1C	NPT520-34 CU-CPT22
3) Gap junction blockers Figure 1D	CBX Gap3211 Gap2409 Gap2605
4) Endocytosis inhibitors Figure 1F	Dynasore Sertraline
5) Autophagy and lysosome inducers Figure 1H	Rapamycin Metformin Trehalose Nilotinib KYP-2407 Ambroxol AR7
6) Misfolding inhibitors Figures 1L,M	NPT200-11 Citr01 EGCG Anle1386 Plant extracts and phytochemicals SynuClean-D Apigenin
7) Lipid-induced aggregation inhibitors Figure 1N	ENT-01 Trodesugenine NPT200-11

EPFL Cell-to-cell transmission, internalization, and trafficking of aSyn and therapeutic targets along the pathways – small molecules



TABLE 3 | Pharmacological approaches to reduce asyn.

Small molecule	Origin	Mechanism of action	Model(s)	Clinical stage	References
<i>Beta2 adreno receptor agonists</i> 1. Metaprotenerol 2. Clenbuterol 3. Salbutamol	Synthetic	Agonists decrease transcription of SNCA gene.	Primary rat neurons; neuron precursors derived from iPSCs from patient with SNCA-triplication. MPTP mice: protected TH+ neurons. WT mice: reduced expression of asyn in SN.	Synucleinopathies: N/A	(215)
4. Salmeterol	Synthetic	Inhibits transcription of pro-inflammatory cytokines	MPTP mice: protected DA neurons against induced toxicity.	N/A	(216)
<i>Disaggregation of asyn</i> 1. NPT200-11 (UCB0599)	Synthetic	Inhibits lipid-dependent nucleation	PONG76 mice: reduced retinal a-syn pathology. Line 6 mouse model: reduced cortical a-syn pathology and astrogliosis, normalized striatal dopamine transporter levels, and improved motor phenotype.	Phase 2 (NCT04658186) in PD patients	(217, 218)
2. Anle138b	Synthetic	Anti-oligomeric	MPTP mice: preserved dopaminergic nigral neurons. Thy1-A30P mice: decreased pathological a-syn oligomers. M12 transgenic mice: reduced density of a-syn aggregates. Improved dopamine neuron function and gait. MSA mice: rescued motor dysfunction, reduced a-syn oligomers and glial cytoplasmic inclusions, preserved DA neurons.	Phase Ib (NCT04685265) in PD patients	(219-221)
3. ENT-01 (squalamine)	Natural	Inhibits lipid-induced asyn aggregation	SHSY5Y cells: reduced asyn oligomer-induced toxicity. C.elegans overexpressing asyn: restored motor dysfunction.	Phase 2b KARMET (NCT03781791) in PD patients. Phase I (NCT03938922) PD dementia	(222)
4. Trodusquemine (MSI-1436)	Natural	Inhibits lipid-induced and fibril-induced asyn aggregation	SHSY5Y cells: reduced oligomer-induced toxicity. C.elegans PD model: reduced asyn inclusions, increased longevity.	N/A	(223)
5. CLR01	Synthetic	Molecular tweezer inhibits asyn aggregation through binding to lysine residues of asyn critical for its oligomerization	Zebra fish-asyn: improved phenotype, and survival, suppressed a-syn aggregation. Thy1-asyn mice: attenuated motor dysfunction, however, did not reduce aggregated a-syn levels. LB treated iPSCs: decreased aggregation and toxicity. LB and pff-seeded mice: reduced asyn pathology and DA neuron rescue.	N/A	(224-226)
6. EGCG	Natural	Inhibits asyn fibrillogenesis, converts fibrils into amorphous, non-toxic protein aggregates.	HEK-293 WT asyn; MPTP mice: rescued motor dysfunction, protected TH+ SN neurons, increased dopamine expression, reduced a-syn. MPTP-monkeys: reduced oligomeric a-syn in striatum, increased nigral TH+ neurons and DA levels, improved motor dysfunction.	Phase 3 completed. PROMESA clinical trial of EGCG in patients with MSA, failed to show a protective effect.	(227-228)

TABLE 1 | Continued

Small molecule	Origin	Mechanism of action	Model(s)	Clinical stage	References
7. Phenylbutyrate	Natural	Histone deacetylase inhibitor, increases DJ-1 production levels.	MPTP mice: protected dopaminergic neurons and preserved motor and cognitive functions. Increased brain a-syn clearance, reduced neuroinflammation.	Completed Phase I (NCT02048434) in PD patients.	(230, 231)
8. SynuClean-D	Synthetic	Binds to fibrils and disrupts their nucleation and elongation.	C.elegans PD models: decreased asyn aggregation, rescued dopaminergic neurodegeneration, and restored motor function.	N/A	(232)
9. Apigenin	Natural	Slows secondary nucleation of asyn.	Cell free assay: reduced number of oligomers formed in asyn aggregation assay.	N/A	(233)
<i>Modulating autophagy</i> 10. KYP-2047	Synthetic	Prolyl oligopeptidase inhibitor	Asyn pff-SHSY5Y cells: increased degradation of HMW asyn, reduced a-syn monomers and a-syn secretion. Cell lines over-expressing mutant a-syn: reduced a-synuclein inclusions, improved cell viability. A30P-asyn mice: reduced soluble a-syn, improved motor symptoms	N/A	(234-236)
11. NPT520-34	Synthetic	Toll-like receptor 2 antagonist. Facilitates clearance of misfolded asyn via upregulating autophagy	LB1 mice: reduced accumulation of a-syn and neuroinflammation, preserved dopamine signaling in brain, improved motor function.	Phase Ib	(172, 237)
<i>Iron related molecules</i> 12. ATH434	Synthetic	Redistributes labile iron	MPTP, 6-OHDA, A53T a-syn mice: protected SNpc neurons, reduced asyn accumulation, improved motor performance. MSA mice: preserved dopaminergic nigral neurons, reduced asyn oligomerization.	Completed Phase I in healthy elder volunteers. Plans for Phase 2.	(238)
13. Synucleozoid	Synthetic	Downregulates SNCA mRNA translation	SHSY5Y cells: reduced asyn pff-induced toxicity, decreased asyn expression.	N/A	(239)

Kevin McFarthing^a, Susan Buff^b, Gary Rafaloff^c, Brian Fiske^d, Leah Mursaleen^e, Rosie Fuest^e, Richard K. Wyse^e and Simon R.W. Stott^{e,*}

Symptomatic Therapy

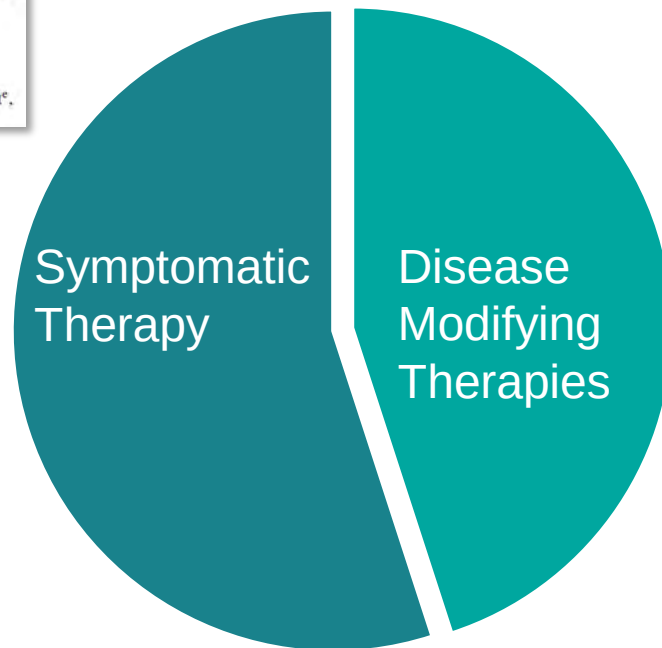


Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update

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139 Clinical Trial

17'000 Patients worldwide



EPFL Current clinical trial in PD ★

Symptomatic therapies

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Symptomatic Therapy

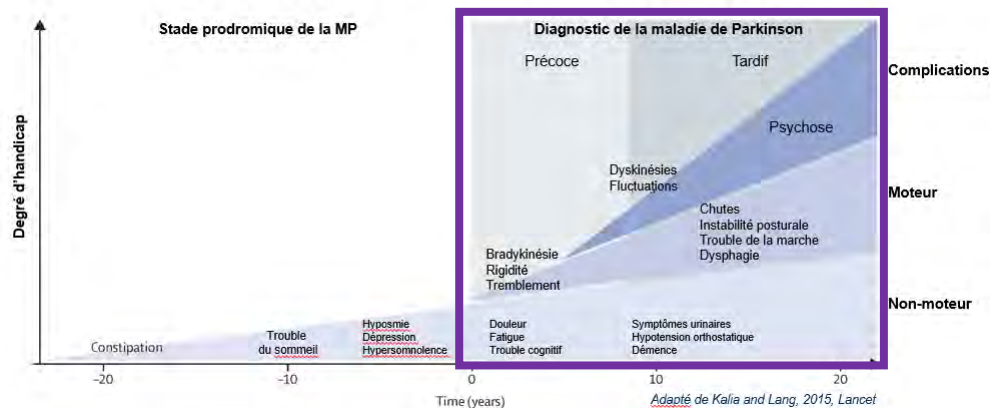
Definition: Symptomatic therapies aim to **relieve or manage the symptoms** associated with a disease without addressing the underlying cause or progression of the disease itself.

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

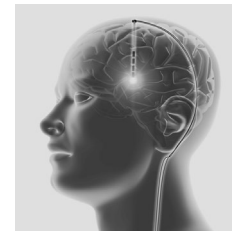
Key Point: Symptomatic therapies **do not halt or slow the progression** of the underlying disease but instead manage the discomfort or limitations it causes.

EPFL Current clinical trial in PD ★

Symptomatic therapies



1. Compensate for dopamine deficiency due to neuronal death through medication (Levodopa, dopamine agonists) to reduce the severity of motor symptoms.
2. Deep Brain Stimulation: Electrical impulses in the thalamus improve neuron communication and reduce motor symptoms (effective in ~10 to 20% of patients).



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.

EPFL 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.



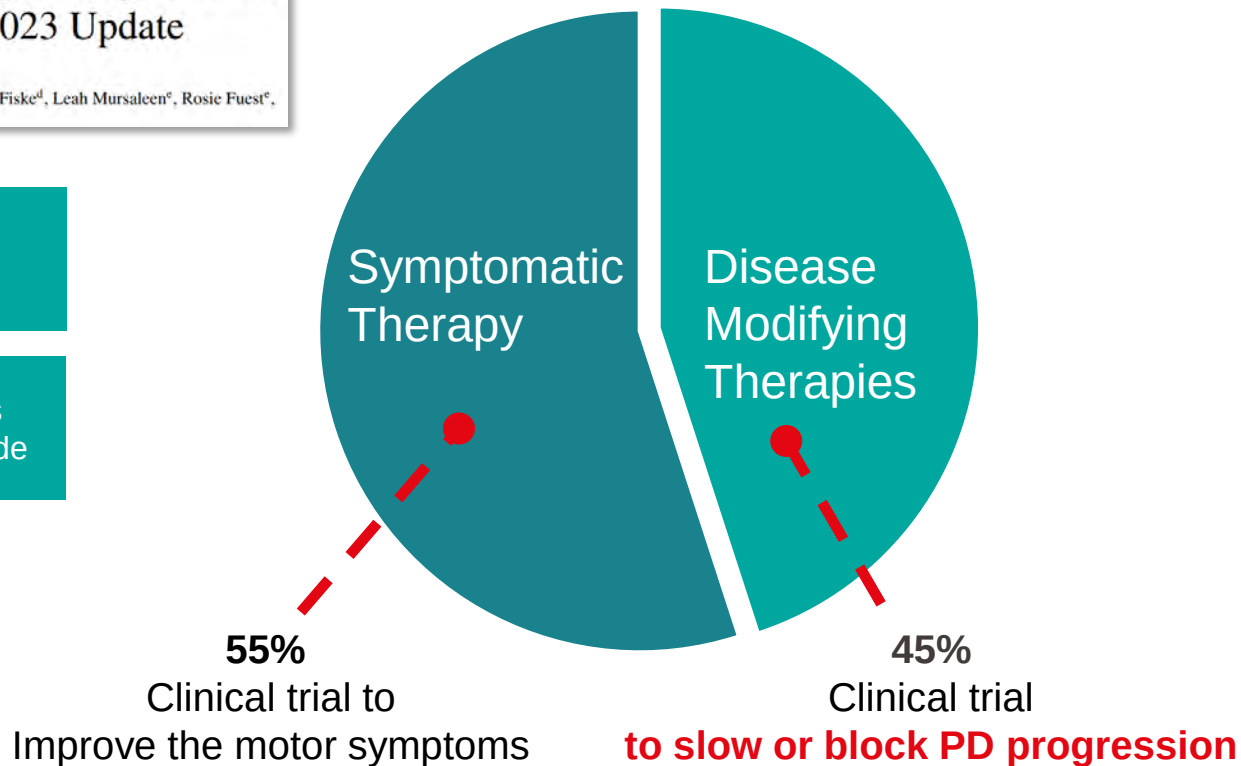
Disease
Modifying
Therapies

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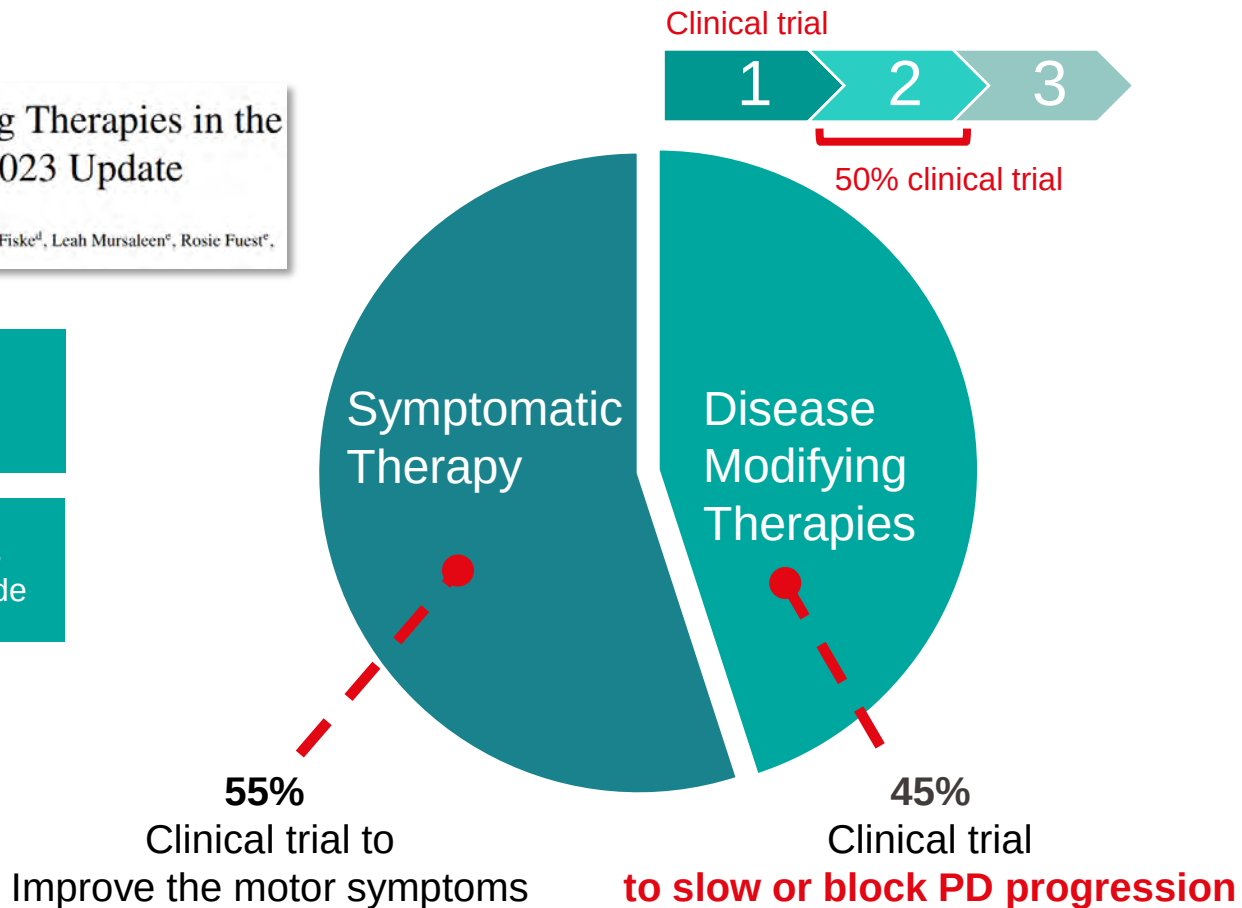


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EPFL PD Medications Currently in Clinical Trials – 2024

Case of drug repurposing

65



Case of drug repurposing

What is 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.



Case of drug repurposing drug ★

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.

Case of drug repurposing drug – GLP1 receptor (Diabetes)

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



Lixisenatide

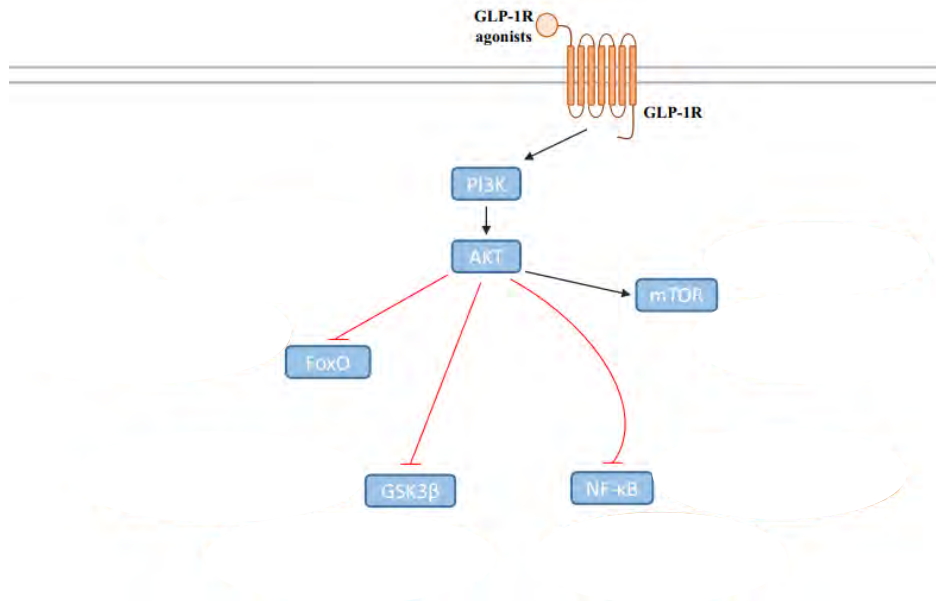


- Encouraging results (slowing of motor symptom progression over a one-year period).
- However, this study needs to be validated in a larger cohort of patients and repeated to assess long-term benefits
- But further studies at the clinical level are block by Sanofi 😊

Case of drug repurposing drug – GLP1 receptor



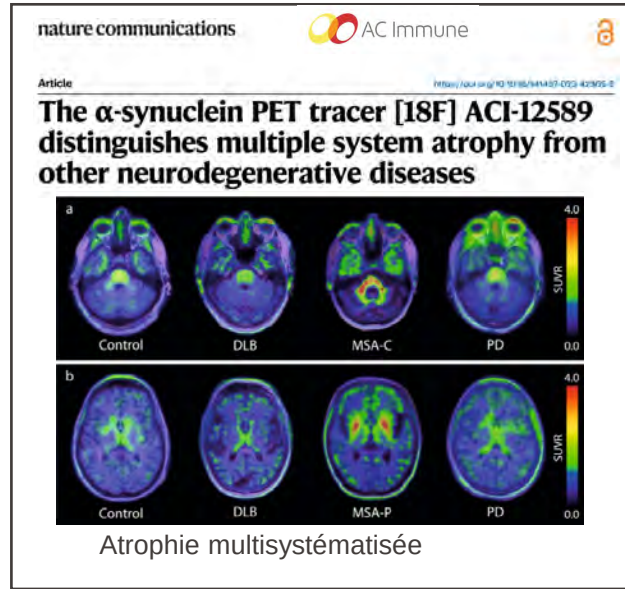
Case of drug repurposing drug – GLP1 receptor



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

Daniella Balduino Victorino¹ · Mariana Nejm¹ · Marcia Guimarães-Marques¹ · Fulvio Alexandre Scorza¹ · Carla Alessandra Scorza¹

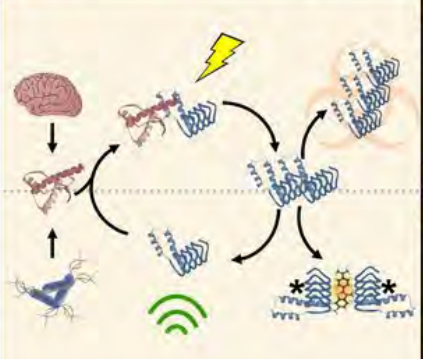
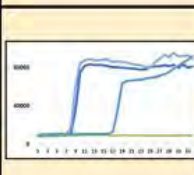
UNDER INVESTIGATION



ACI-15916: Next generation a-syn tracer for AC Immune



- I. Modeling neurodegenerative disorders (NDDs) in the Lab
- II. Drugs therapy in Clinical trials
- III. Bench techniques applied to early diagnosis (exercices part)**

	Assay-specific conditions	Mechanism of detection	Diagnostic Visualization
Antibody-antigen interactions	IHC Acid pretreatment, enzymatic digestion, antigen exposure using fixed, prepared tissues		
	WB Enzymatic digestion of fresh or fixed tissue homogenates; gel separated and adhered to a membrane		
	ELISA Enzymatic digestion or proprietary binding components using fresh tissue homogenates		
Seeded amplification	PMCA Sonication, whole brain homogenate, western blot readout		
	RT-QuIC Shaking, recombinant protein, real time fluorescent readout		

Pro and con of each assay explained in the Biomarker exercise ★

See exercise in the Moodle

“Biomarkers exercise”

➔ *Detailed explanations of the pro and cons of each assays*

(WB, ELISA, IHC, SAA)

