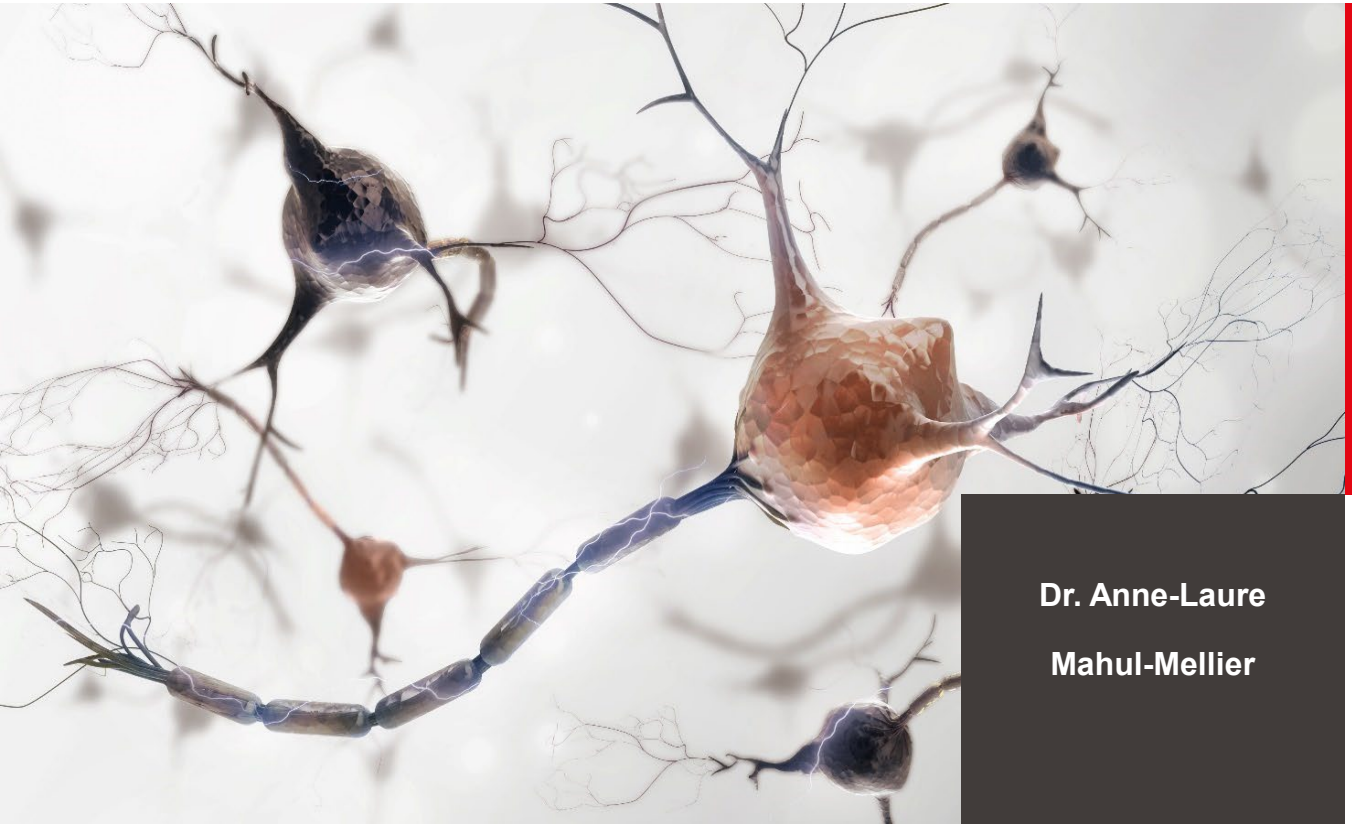


Personalized medicine in NDDs

Dr. Anne-Laure Mahul-Mellier

6 Master internships (starting Feb/March 2026):

AC Immune

https://www.acimmune.com/careers/join-us/#job-opportunities

INTERNSHIP H1 2026 – PHARMACOKINETICS

AC Immune is looking for a trainee to support the profiling of SME compounds based on Pharmacokinetic properties. Start date: February or March 2026 for 6 months

INTERNSHIP H1 2026 - NEUROINFLAMMATION

AC Immune R&D team is seeking a highly motivated trainee to support the discovery and development of new drugs for the treatment of neurodegenerative and inflammatory diseases. Start Date: February or March 2026 for 6 months

INTERNSHIP H1 2026 - TDP-43

AC Immune R&D team is seeking a highly motivated trainee to support the discovery and development of new drugs for the treatment of neurodegenerative and inflammatory diseases. Start Date: February or March 2026 for 6 months

INTERNSHIP H1 2026 - ANTIBODY ENGINEERING

AC Immune is seeking a highly motivated trainee to join the Antibody Engineering Team, with the goal of humanizing and optimizing an antibody for intracellular targeting. Start Date: February 2026 for 6 months

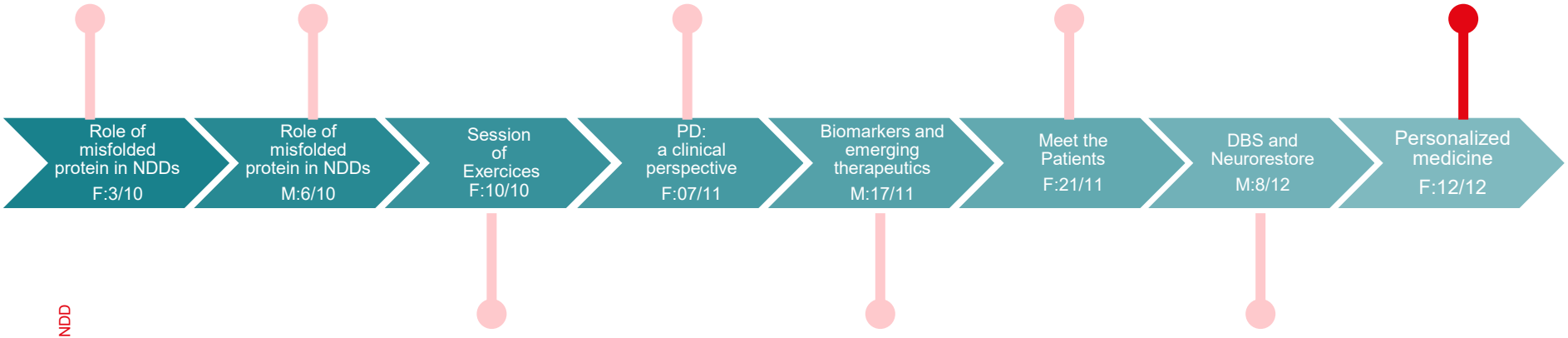
INTERNSHIP H1 2026 - DATA SCIENCE

The Data Science, Engineering, and AI team is seeking a motivated student to apply data analysis, and statistical techniques to various projects. Start Date: February or March 2026 for 6 months

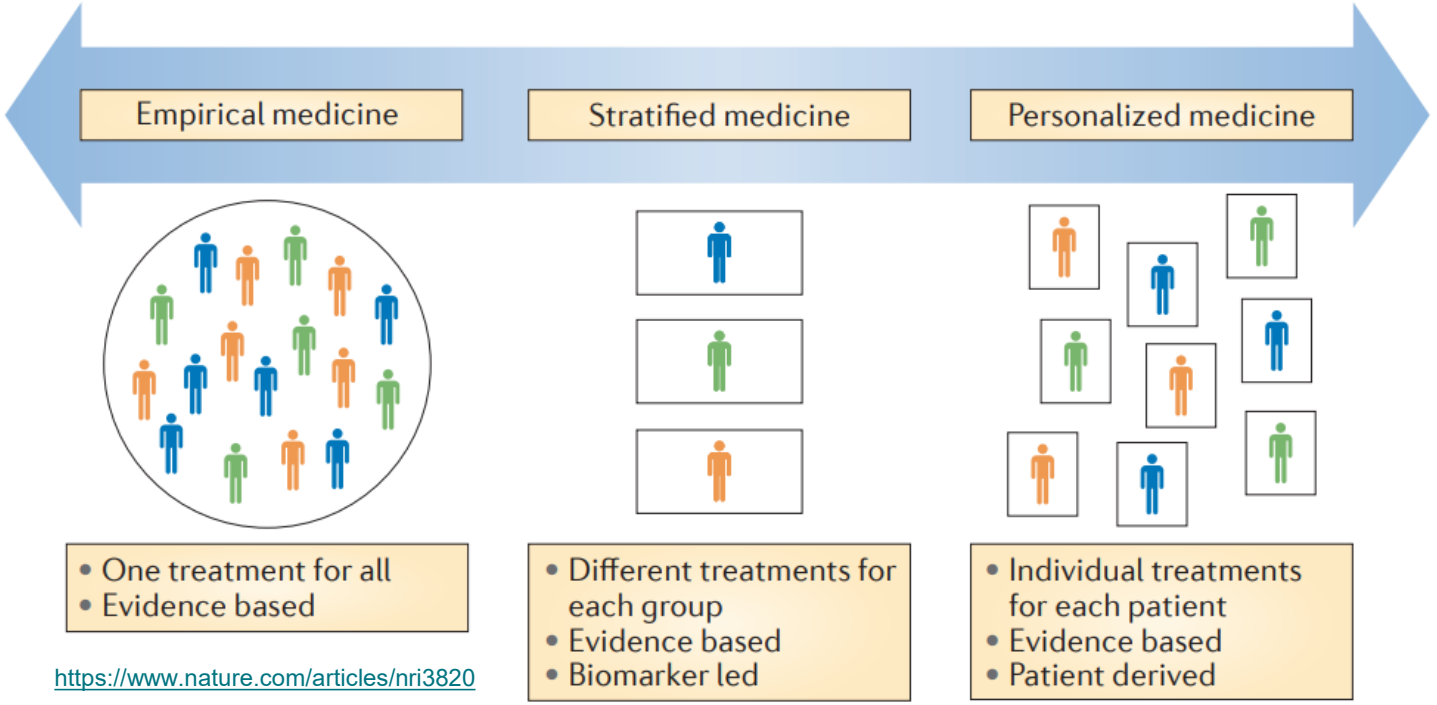
INTERNSHIP H1 2026 – ACTIVE IMMUNOTHERAPY

AC Immune is seeking a motivated student to work within the R&D team in collaboration with the Data Science team. Start date: February or March 2026 for 6 months

Course organisation:



Personalized/precision medicine: ★
Definition



https://www.nature.com/articles/nri3820

Personalized medicine = delivering the right treatment to the right patient at the right time, based on their unique biological, genetic, environmental, and lifestyle characteristics.

Brainstorming Challenge:

Why One-Size-Fits-All cannot work to treat NDDs? And why shall we consider personalized medicine for NDDs?

- List all the reasons you can think of on the table (next slide).
- Be as broad as possible !!!

Brainstorming Challenge:

Why One-Size-Fits-All cannot work to treat NDDs? And why shall we consider personalized medicine for NDDs?

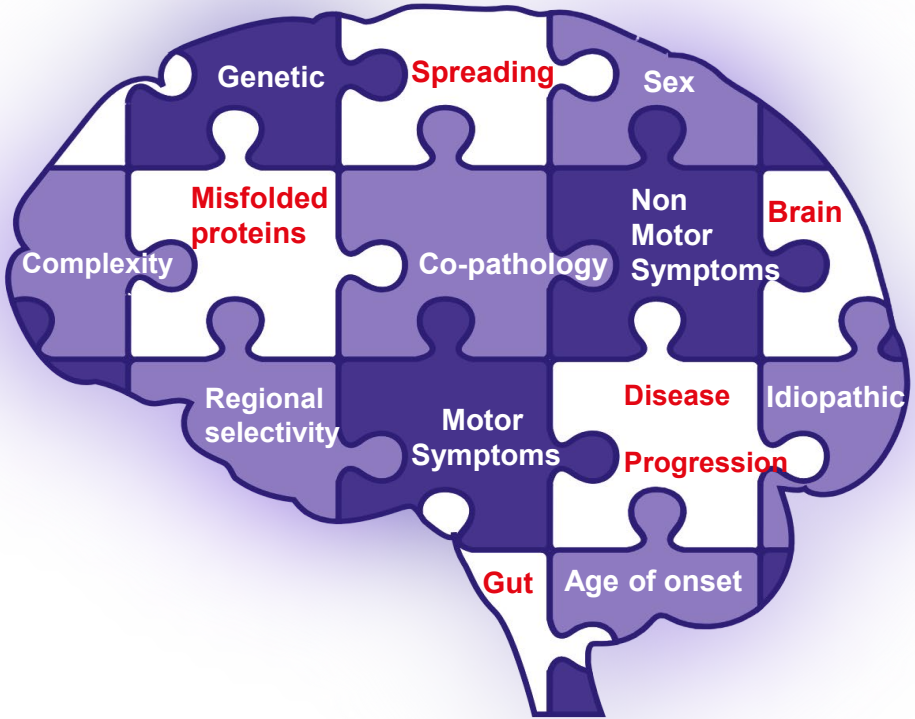
Category	Examples / Key Points	Why It Prevents One-Size-Fits-All

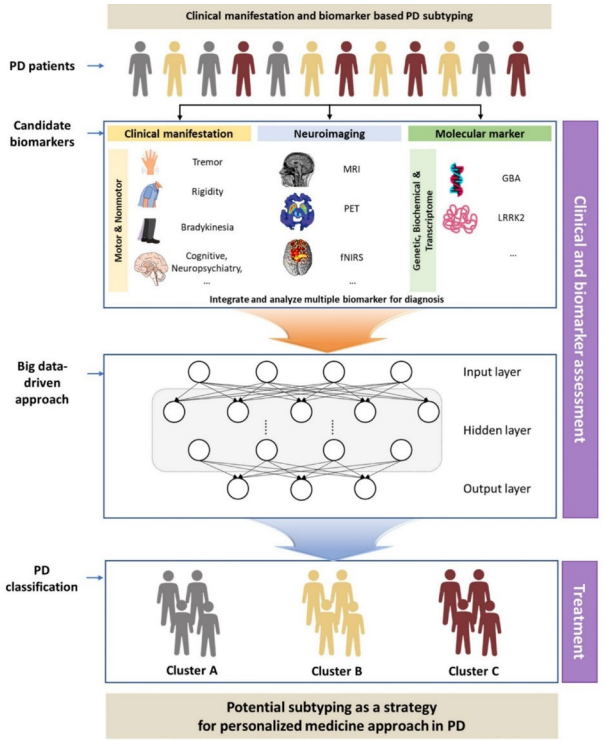
Brainstorming Challenge: ★

Why One-Size-Fits-All cannot work to treat NDDs? personalized medicine for NDDs?

Category	Examples / Key Points (Within a Disease)	Why It Prevents One-Size-Fits-All Treatments
Diagnostic uncertainty and mixed pathologies	Even within one diagnostic label (e.g., PD, AD), patients may present overlapping or mixed pathologies (e.g., Lewy pathology + Tau pathology; AD: tau + amyloid; PD patients without typical Lewy bodies; variable patterns of neurodegeneration).	A drug designed for one pathological process may not work in patients whose disease is driven by a different or mixed pathology.
Clinical heterogeneity	Same disease label but very different clinical presentations: motor-dominant vs non-motor–dominant PD; amnestic vs language-led AD; variable cognitive, autonomic, sensory, or behavioral symptoms.	Clinical subtypes reflect underlying biological differences → they respond differently to the same therapy.
Disease stage heterogeneity	Long prodromal phases; early vs moderate vs late disease; different degrees of neuronal loss at diagnosis.	Many therapies work only at specific stages (e.g., early neuroprotection vs late symptomatic treatment).
Disease initiation variability	Some patients show early peripheral or autonomic involvement; others show initial cortical or subcortical involvement.	Distinct initiation routes lead to different trajectories and therapeutic windows.
Microbiota dysbiosis	Individual differences in gut microbiota composition influence inflammation, immune tone, metabolite production, and even drug metabolism.	Microbiome-dependent variability changes disease risk, symptoms, progression, and response to medication.
Environmental & lifestyle factors	Exposure to toxins, trauma, diet, sleep, exercise, stress, and cognitive reserve differ between individuals.	Environmental profiles interact with biology, modifying disease course and altering therapeutic needs.
Genetic heterogeneity	Patients with the same clinical diagnosis may carry different genetic variants (e.g., LRRK2 vs GBA vs idiopathic PD; APOE4 vs non-APOE4 AD).	Different genetic drivers create distinct biological subtypes requiring distinct therapeutic strategies.
Epigenetic variability	Aging, environment, and cell stress modify DNA methylation and chromatin state differently across individuals.	Epigenetic differences alter vulnerability, neuronal function, and treatment responsiveness.
Molecular / pathological heterogeneity	Within a single disease, different patients may show varying degrees of protein aggregation, mitochondrial stress, lysosomal dysfunction, inflammation, synaptic deficits, or combinations thereof.	A therapy targeting only one pathological mechanism will not benefit patients whose disease is driven by another mechanism.
Misfolded protein diversity ("strains")	Patients with the same proteinopathy may carry different conformational variants of the misfolded protein (e.g., distinct aSyn, tau, or TDP-43 structural forms).	Antibodies or small molecules effective against one structural variant may not affect others.
Cell-type and regional vulnerability	The sequence and extent of neuronal loss differ across patients: e.g., in PD some lose dopaminergic neurons early, others show early cortical or autonomic involvement.	Therapies must match the affected circuits; different patterns need different interventions.
Comorbidities	Cardiovascular disease, diabetes, immune dysfunction, psychiatric symptoms, sleep disorders vary greatly between patients.	Comorbidities strongly modulate progression and modify benefit/risk of treatments.
Treatment response variability	Differences in metabolism, blood–brain barrier permeability, immune reactivity, microbiome–drug interactions, side-effect susceptibility.	The same drug dose or mechanism yields very different efficacy and safety profiles across individuals.

Why personalized medicine matters in NDDs?





Most NDD clinical trials failed not because the drug was bad or the pre-clinical model was not good enough, but because 1) clinical trials are done at a late stage of the disease, not at early stages, as we do not have biomarkers for early diagnosis, and 2) the trial grouped together completely different biological subtypes. Personalized medicine aims to fix the issue of cohort stratification.

Where personalized medicine acts in NDDs?

- **Personalized disease modeling** → iPSCs
- **Personalized tissue architecture** → Organoids
- **Personalized stratification & early detection** → AI + biomarkers
- **Personalized therapeutics** → genotype-based therapies, cell therapy
- **Personalized follow-up** → digital biomarkers, wearables

To personalize treatment, we first need personalized *models* of disease

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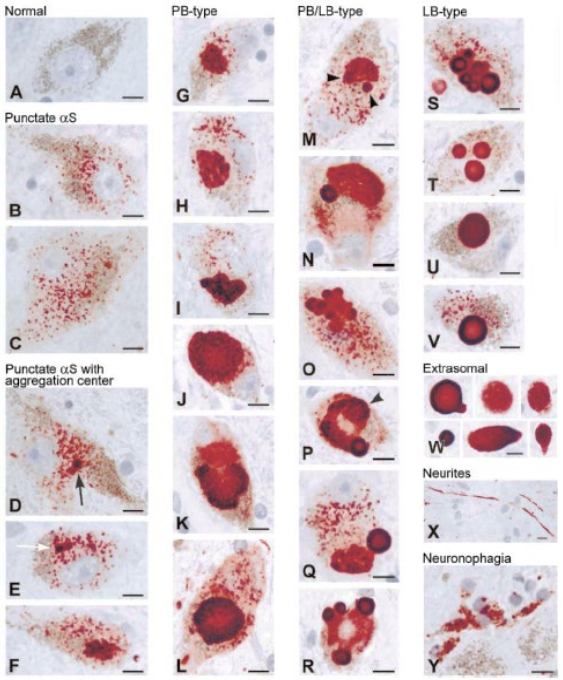
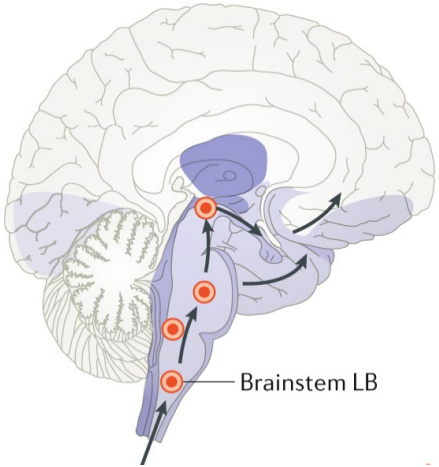
To personalize treatment, we first need personalized *models* of disease

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

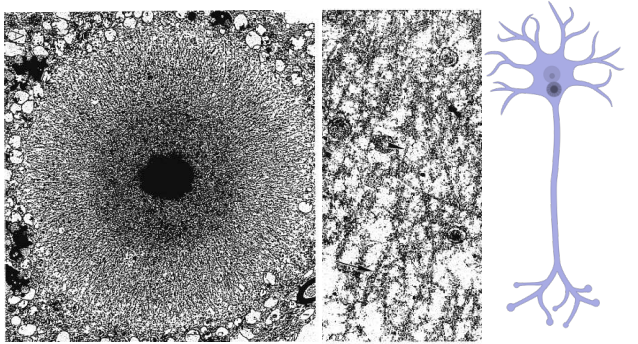


Kuusisto et al, 2003

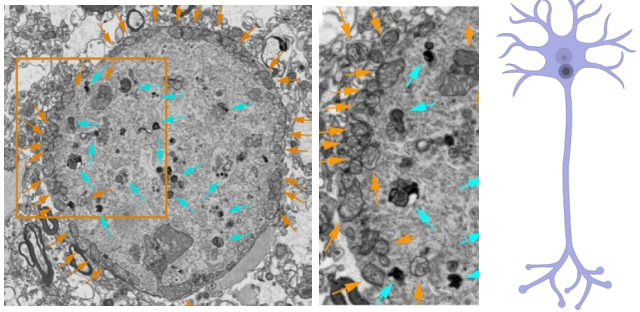


Fares et al., 2020

Brainstem LB



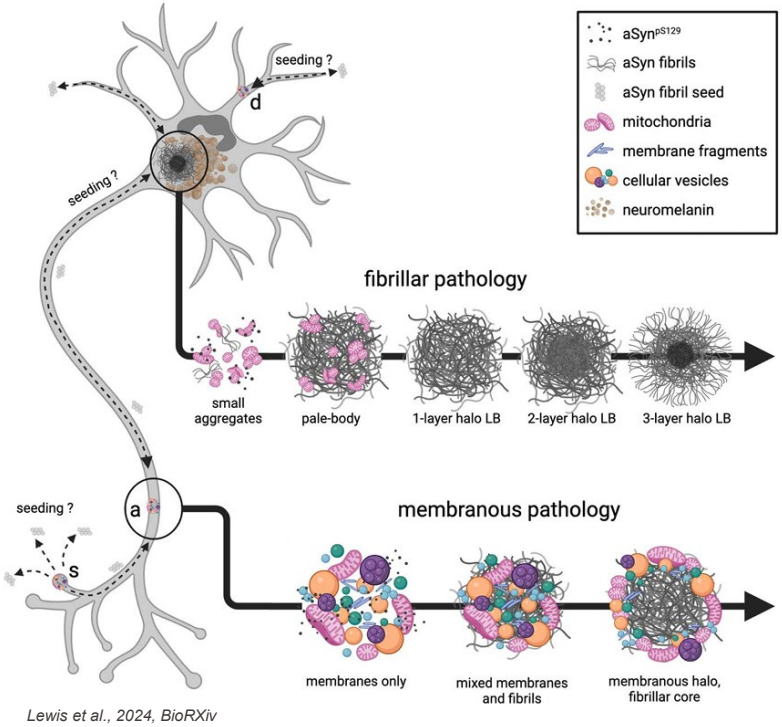
Forno et al, 1996



Shahmoradian and Lewis et al., 2019

- *Why such heterogeneity? Continuum of morphologies? Co-existing?*
- *What determines why the same type of neurons develop morphologically distinct LBs? Cellular and molecular factors?*

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



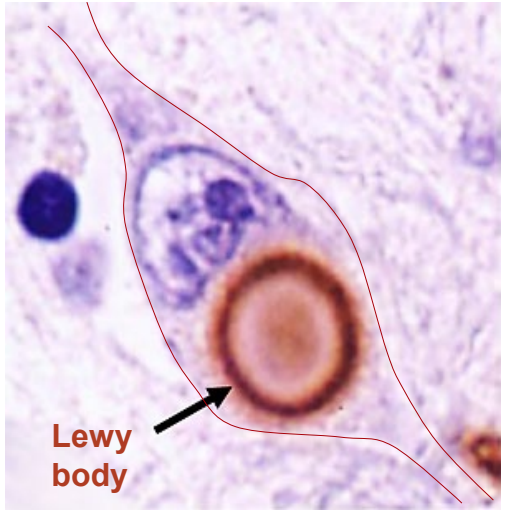
Lewis et al., 2024, BioRXiv

Answering this question requires the development of cellular or animal models that recapitulate <u>the process of LB formation</u>

Developing cellular and In vivo models reflecting human pathology

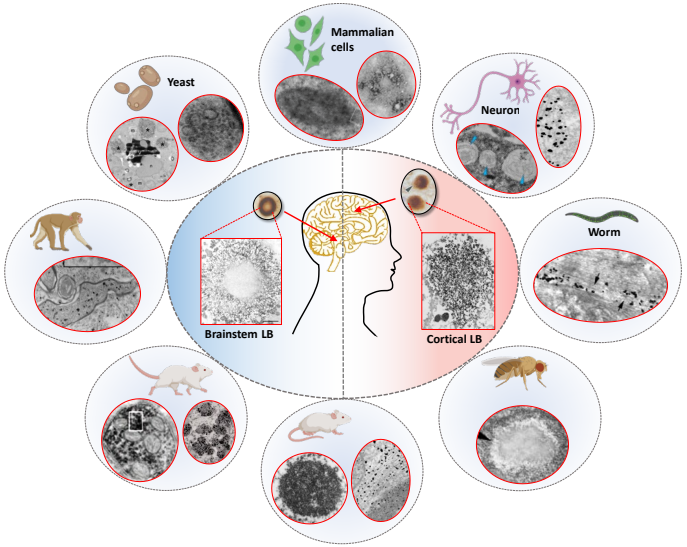
Toward more predictive preclinical studies

Neuron from patients
affected by Parkinson's disease



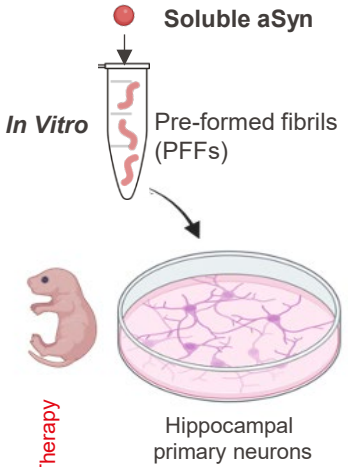
≠

Available
cellular and animal models



Limitations:
Existing cellular and animal models do not replicate the biochemical and ultrastructural properties of Lewy bodies formed in the brains of human patients.

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

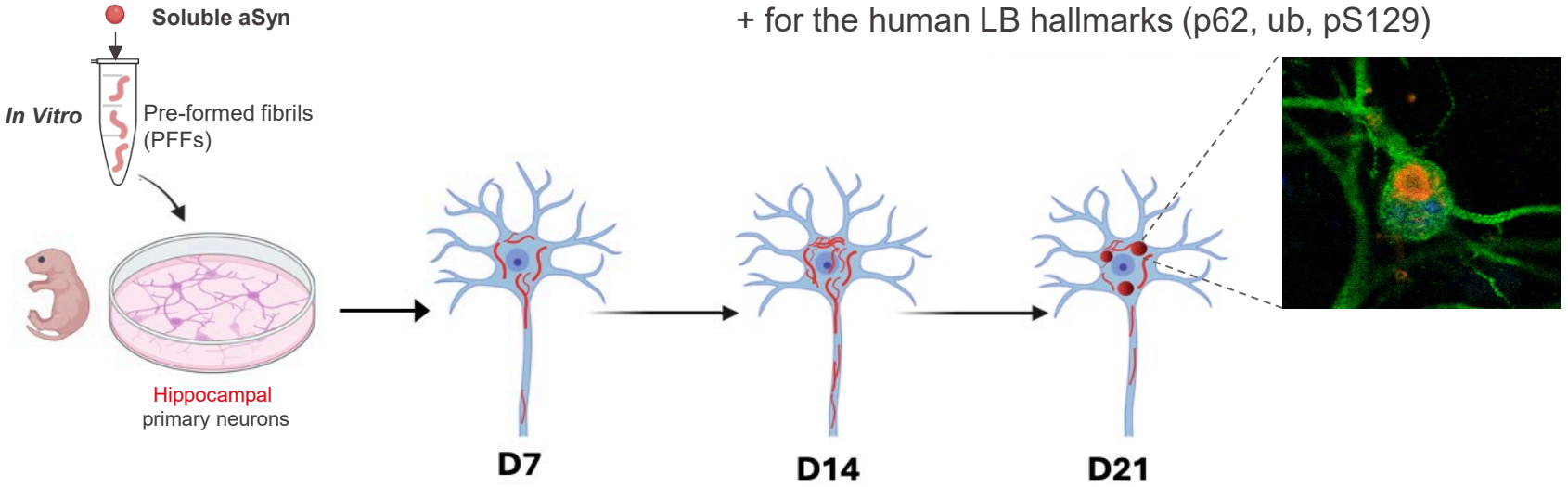


Neuron Article

Exogenous α-Synuclein Fibrils Induce Lewy Body Pathology Leading to Synaptic Dysfunction and Neuron Death

Laura A. Volpicelli-Daley,[1] Kelvin C. Luk,[1] Tapan P. Patel,[2] Selcuk A. Tanik,[1] Dawn M. Riddle,[1] Anna Stieber,[1] David F. Meaney,[2] John Q. Trojanowski,[1] and Virginia M.-Y. Lee[1,*]
[1]Department of Pathology and Laboratory Medicine, Institute on Aging and Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA
[2]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA
*Correspondence: vmylee@upenn.edu
DOI 10.1016/j.neuron.2011.08.033

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



+ for the human LB hallmarks (p62, ub, pS129)

Research scope

Neuron Article

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[1]Department of Pathology and Laboratory Medicine, Institute on Aging and Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104 USA
[2]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA 19104, USA
*Correspondence: vmylee@upenn.edu
DOI 10.1016/j.neuron.2011.08.033

PNAS

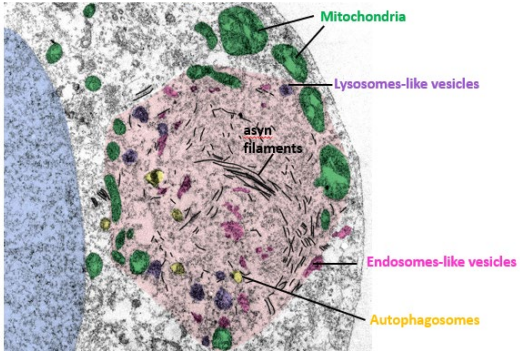
The process of Lewy body formation, rather than simply α-synuclein fibrillization, is one of the major drivers of neurodegeneration

Anne-Laure Mahul-Mellier[a], Johannes Burtscher[a], Niran Maharjan[a], Laura Weerens[a], Marie Croisier[b], Fabien Kuttler[a], Marion Leleu[d,e], Graham W. Knott[b], and Hilal A. Lashuel[a,1]

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

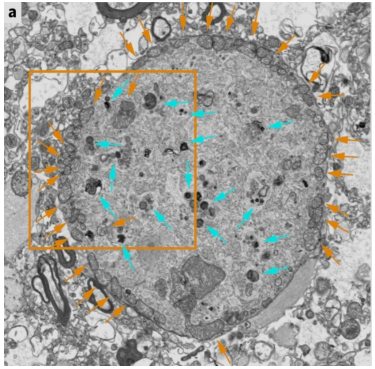
Ultrastructure

Lewy bodies in primary neurons



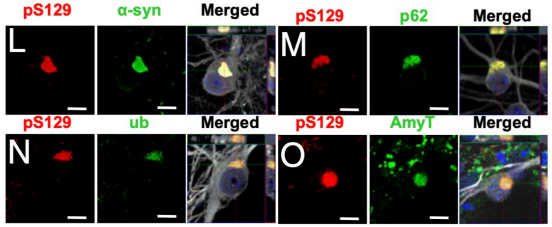
Mahul-Mellier at al., 2020, PNAS

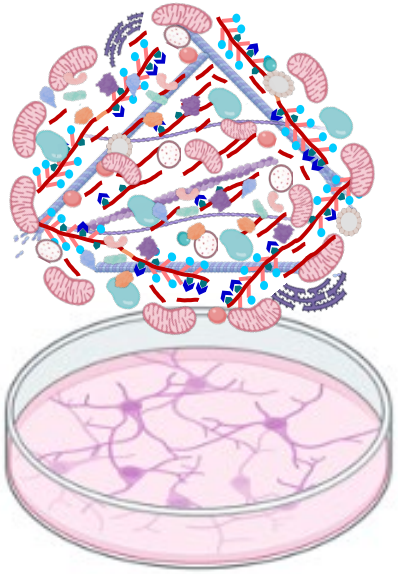
Lewy body in patients



Shahmoradian et al., Nature Neurosciences, 2019

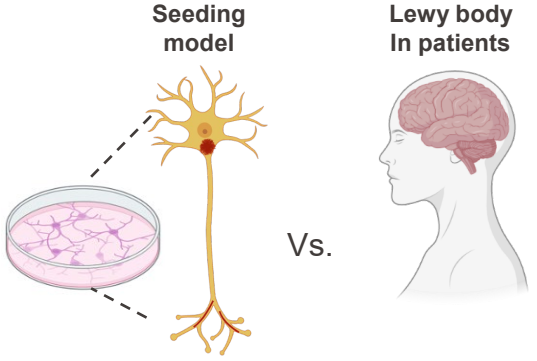
LBs markers



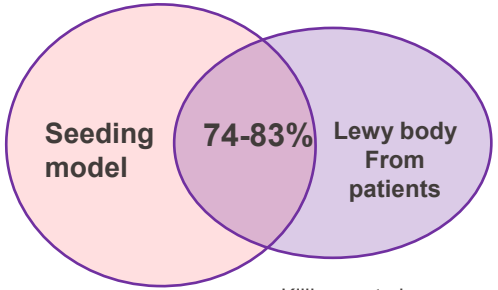


Lewy body in a dish

Proteomics



Proteomic comparison



Mahul-Mellier et al.

Killinger et al.
Xia et al.
Licket et al.
Datta et al.

Research scope

The neuronal Lewy body model:
A platform for drug screening

Testing
novel
therapeutic targets

Libraries of small molecules

Immunotherapies

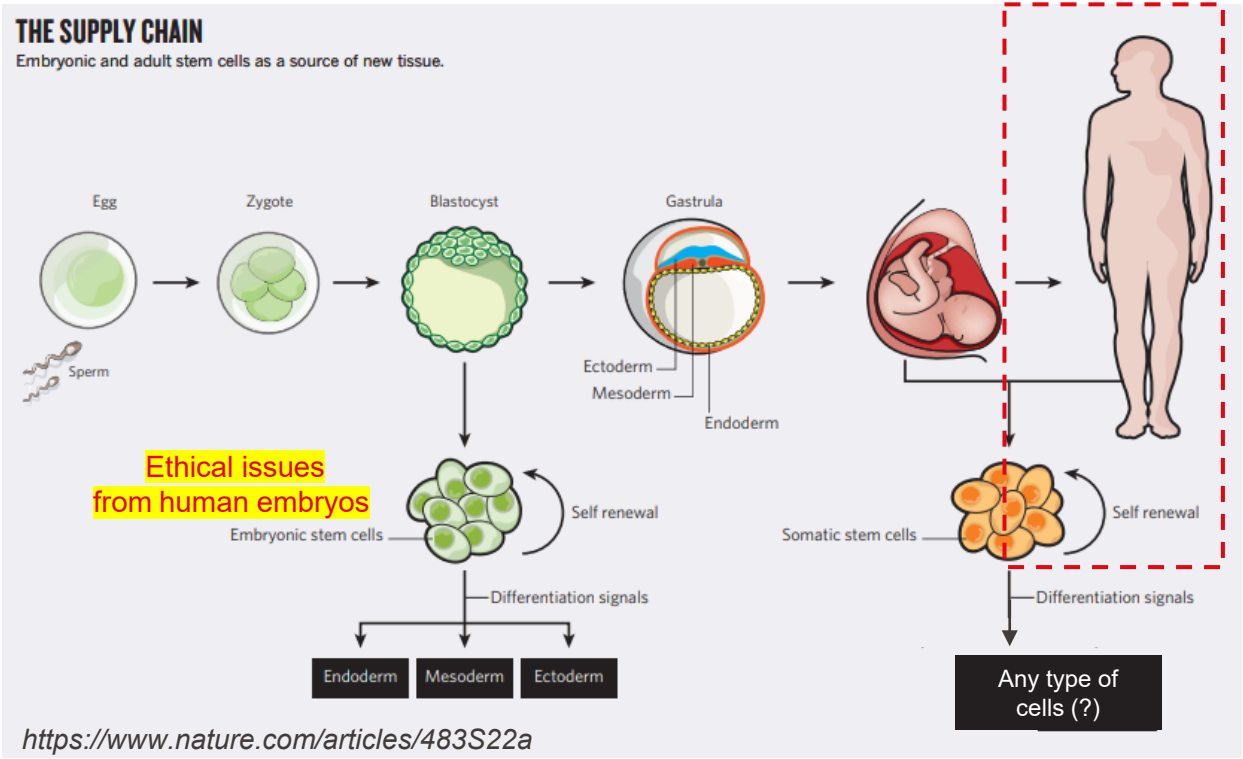
Venoms

Limitations of the model:

1. Mouse aSyn ≠ Human aSyn (by 7 a.a)
2. Does not recapitulate the full biochemical and morphological diversity of PD pathology (e.g: PTMs other than pS129 are absent)
3. Short-timeline (28 days):
   Not suitable to study late stages of LB formation or LB Clearance or their toxicity

How can we translate our cellular rodent models in human neurons ?

Where can we find stem cells in human?

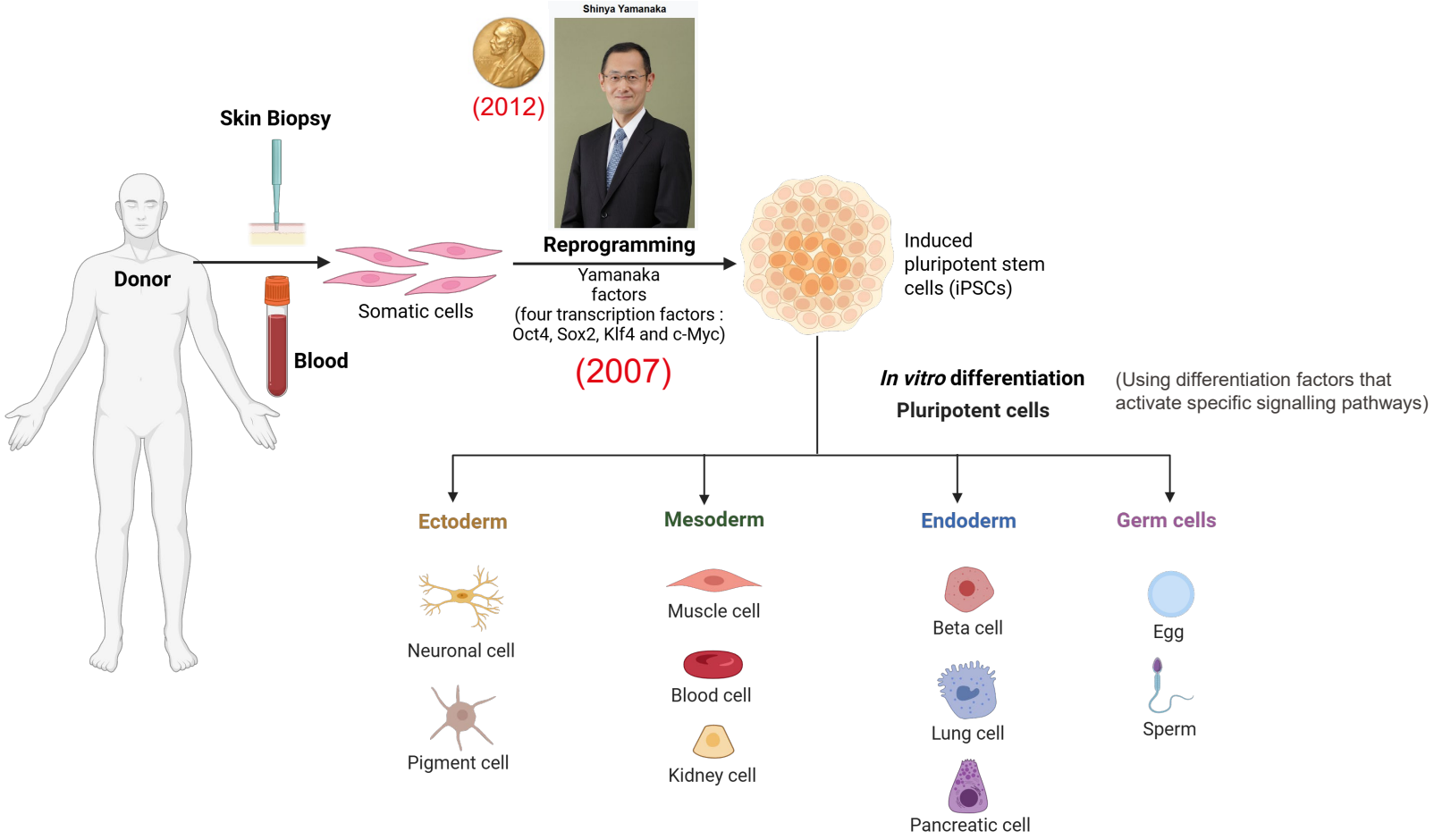


Source: Human (adult)
(no ethical issues)

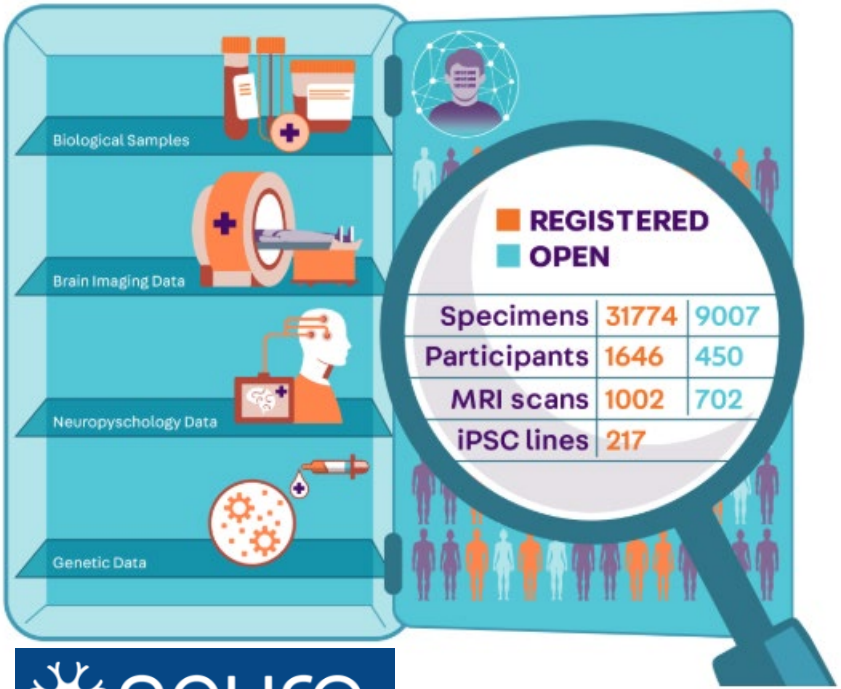
Best somatic cells
➔ fibroblasts

★ A **toti**potent stem cell can give rise to **all (toti)** cell types of the body.
A **pluri**potent stem cell can give rise to **many (pluri)** cell types of the body.
Somatic cells are all the cells in a multicellular organism **except** the reproductive cells (sperm and egg).

The induced pluripotent stem cell (iPSC) technology ★



Source of iPSCs: Biobanks



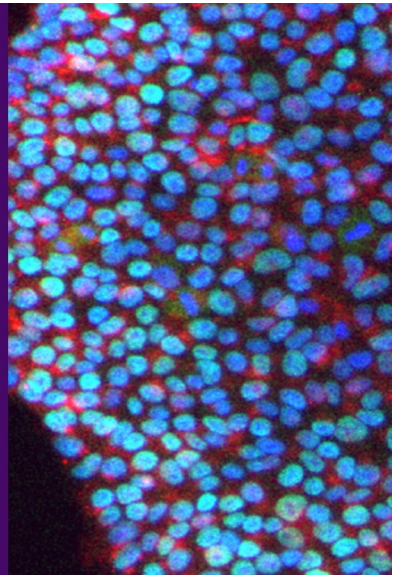
neuro
Montreal Neurological Institute-Hospital
Tanenbaum Open Science Institute

The Neuro's Early Drug Discovery Unit

iPSC Catalog

Last modified: July 2025

C-BIG



Source of iPSCs: Biobanks

PARKINSON'S DISEASE							
CELL LINE NAME	CELL LINE STATUS	SEX	PATIENT AGE (years)	MATERIAL SOURCE	TYPE OF REPROGRAMMING	GENE AFFECTED	PRIMARY DISEASE MUTATION
IPSC0094	Ready to Ship	MALE	70	PBMC	EPISOMAL	SPORADIC PD	NA
IPSC0042	Ready to Ship	FEMALE	61	PBMC	EPISOMAL	SPORADIC PD	NA
IPSC0047	Ready to Ship	MALE	67	PBMC	EPISOMAL	SPORADIC PD	NA
IPSC0021	Ready to Ship	FEMALE	UNK	PBMC	EPISOMAL	PARKIN	Homozygous deletion between exon 3 and 4
IPSC0050	Ready to Ship	MALE	54	PBMC	EPISOMAL	LRRK2	R1441H
IPSC0051	Ready to Ship	MALE	54	PBMC	EPISOMAL	LRRK2	R1441H (corrected)
IPSC0048	Ready to Ship	MALE	76	PBMC	EPISOMAL	LRRK2	M1646T
IPSC0017	Ready to Ship	FEMALE	64	PBMC	EPISOMAL	LRRK2	M1646T
IPSC0018	Ready to Ship	FEMALE	64	PBMC	EPISOMAL	LRRK2	M1646T(corrected)
IPSC0006	Ready to Ship	FEMALE	62	PBMC	EPISOMAL	LRRK2	G2019S
IPSC0007	Ready to Ship	FEMALE	62	PBMC	EPISOMAL	LRRK2	G2019S (Corrected)
IPSC0003	Ready to Ship	FEMALE	74	PBMC	EPISOMAL	LRRK2	G2019S
IPSC0037	Ready to Ship	FEMALE	65	PBMC	EPISOMAL	LRRK2	G2385R
IPSC0039	Ready to Ship	FEMALE	65	PBMC	EPISOMAL	LRRK2	G2385R(corrected)
IPSC0040	Ready to Ship	FEMALE	58	PBMC	EPISOMAL	LRRK2	intron variant rs41286460
IPSC0041	Ready to Ship	FEMALE	58	PBMC	EPISOMAL	LRRK2	N551K-R1398H-K1423K (protective haplotype)
IPSC0058	Ready to Ship	MALE	66	PBMC	EPISOMAL	LRRK2	N551K-R1398H-K1423K (protective haplotype)
IPSC0059	Ready to Ship	MALE	66	PBMC	EPISOMAL	LRRK2	N551K(corrected)-R1398H-K1423K (protective haplotype)
IPSC0060	Ready to Ship	MALE	66	PBMC	EPISOMAL	LRRK2	N551K-R1398H(corrected)-K1423K (protective haplotype)
IPSC0020	Available upon Request	FEMALE	90	PBMC	EPISOMAL	LRRK2	N551K-R1398H-K1423K (protective haplotype)
IPSC0052	Available upon Request	MALE	64	PBMC	EPISOMAL	LRRK2	N551K-R1398H-K1423K (protective haplotype)
IPSC0004	Ready to Ship	FEMALE	65	PBMC	EPISOMAL	GBA1	N370S
IPSC0005	Ready to Ship	FEMALE	65	PBMC	EPISOMAL	GBA1	N370S (corrected)
IPSC0001	Ready to Ship	FEMALE	62	PBMC	EPISOMAL	GBA1	W378G
IPSC0002	Ready to Ship	FEMALE	62	PBMC	EPISOMAL	GBA1	W378G (corrected)
IPSC0027	Ready to Ship	FEMALE	46	PBMC	EPISOMAL	GBA1	L324I
IPSC0055	Ready to Ship	MALE	59	PBMC	EPISOMAL	GBA	E326K
IPSC0056	Ready to Ship	MALE	59	PBMC	EPISOMAL	GBA	E326K (corrected)
IPSC0053	Ready to Ship	MALE	58	PBMC	EPISOMAL	GBA	L444P
IPSC0054	Ready to Ship	MALE	58	PBMC	EPISOMAL	GBA	L444P (corrected)
IPSC0008	Ready to Ship	FEMALE	64	PBMC	EPISOMAL	TMEM175	Q65P heterozygous
IPSC0009	Ready to Ship	FEMALE	64	PBMC	EPISOMAL	TMEM175	Q65P(corrected)

ALS							
CELL LINE NAME	CELL LINE STATUS	SEX	PATIENT AGE (years)	MATERIAL SOURCE	TYPE OF REPROGRAMMING	GENE AFFECTED	PRIMARY DISEASE MUTATION
IPSC0028	Ready to Ship	FEMALE	46	PBMC	EPISOMAL	SOD1	I114T
IPSC0029	Ready to Ship	FEMALE	46	PBMC	EPISOMAL	SOD1	I114T (Corrected)
IPSC0031	Ready to Ship	FEMALE	42	PBMC	EPISOMAL	SOD1	I114T
IPSC0093	Ready to Ship	MALE	62	PBMC	EPISOMAL	SOD1	I114T
IPSC0015	Ready to Ship	FEMALE	50	PBMC	EPISOMAL	SOD1	I114T
IPSC0014	Available upon Request	FEMALE	22	PBMC	EPISOMAL	SOD1	A4E
IPSC0049	Available upon Request	MALE	66	PBMC	EPISOMAL	C9ORF72	Expansion mutation
IPSC0019	Ready to Ship	FEMALE	80	PBMC	EPISOMAL	VAPB	A2V
IPSC0026	Ready to Ship	FEMALE	81	PBMC	EPISOMAL	sALS	NA
IPSC0030	Ready to Ship	FEMALE	65	PBMC	EPISOMAL	SALS+FTD	NA
IPSC0091	Ready to Ship	MALE	53	PBMC	EPISOMAL	sALS	NA
IPSC0092	Ready to Ship	MALE	49	PBMC	EPISOMAL	sALS, progressed from PLS	NA
IPSC0032	Ready to Ship	FEMALE	77	PBMC	EPISOMAL	sALS	NA
IPSC0057	Ready to Ship	MALE	88	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	FEMALE	80	PBMC	EPISOMAL	VAPB	A2V
ID to be assigned	Ready to Ship	MALE	78	PBMC	EPISOMAL	C9ORF72	C9ORF72 expansion
ID to be assigned	Ready to Ship	MALE	67	PBMC	EPISOMAL	C9ORF72	C9ORF72 expansion
ID to be assigned	Ready to Ship	FEMALE	58	PBMC	EPISOMAL	C9ORF72	C9ORF72 expansion
ID to be assigned	Ready to Ship	FEMALE	47	PBMC	EPISOMAL	C9ORF72	C9ORF72 expansion
ID to be assigned	Ready to Ship	FEMALE	52	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	FEMALE	53	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	MALE	69	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	MALE	60	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	FEMALE	66	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	MALE	59	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	MALE	61	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	MALE	33	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	FEMALE	62	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	FEMALE	54	PBMC	EPISOMAL	sALS	NA
ID to be assigned	Ready to Ship	FEMALE	59	PBMC	EPISOMAL	Multiple System Atrophy	NA

3 pages of iPSCs for PD

*PBMC = Peripheral Blood Mononuclear Cells

iPSCs can be edited with CRISPER

CRISPR KI and ISOGENIC CONTROLS						
CELL LINE NAME	CELL LINE STATUS	GENE EDITED	GENETIC MODIFICATION	EDITING TYPE	ENSEMBL ID	PARENT CELL LINE
IPSC0080	Ready to Ship	SNCA	A30P	KI	ENSG00000145335	IPSC0063
IPSC0081	Ready to Ship	SNCA	A53T	KI	ENSG00000145335	IPSC0063
IPSC0082	Ready to Ship	SNCA	E46K	KI	ENSG00000145335	IPSC0063
IPSC0084	Ready to Ship	SOD1	G93A	KI	ENSG00000142168	IPSC0063
IPSC0065	Ready to Ship	MAPT	P301L	KI	ENSG00000186868	IPSC0063
IPSC0074	Ready to Ship	Parkin	W403A	KI	ENSG00000185345	IPSC0063
IPSC0073	Ready to Ship	Parkin	A401D	KI	ENSG00000185345	IPSC0063
IPSC0075	Ready to Ship	Parkin	Y143D	KI	ENSG00000185345	IPSC0063
IPSC0076	Ready to Ship	Parkin	V393D	KI	ENSG00000185345	IPSC0063
IPSC0071	Ready to Ship	PINK1	C-terminal FLAG tag	KI	ENSG00000158828	IPSC0063
IPSC0109	Ready to Ship	FUS	H517Q	KI	ENSG00000089280	IPSC0063
IPSC0089	Ready to Ship	TARDBP	A382T	KI	ENSG00000120948	IPSC0063
IPSC0090	Ready to Ship	TARDBP	G348C	KI	ENSG00000120948	IPSC0063
ID to be assigned	Available upon Request	LRRK2	G2019S	iso	ENSG00000188906	IPSC0003
IPSC0060	Available upon Request	LRRK2	R1398H	iso	ENSG00000188906	IPSC0059
ID to be assigned	Available upon Request	LRRK2	N551K	iso	ENSG00000188906	IPSC0052
ID to be assigned	Available upon Request	LRRK2	R1398H	iso	ENSG00000188906	IPSC0052
ID to be assigned	Available upon Request	GBA	E326K homo	KI	ENSG00000177628	IPSC0063
ID to be assigned	Available upon Request	GBA	N370S homo	KI	ENSG00000177628	IPSC0063
ID to be assigned	Available upon Request	GBA	L444P	KI	ENSG00000177628	IPSC0063
ID to be assigned	Available upon Request	GBA	T369M	iso	ENSG00000177628	IPSC0011
ID to be assigned	Available upon Request	GBA	rs3115534 G/G homo	KI	ENSG00000177628	IPSC0063
ID to be assigned	Available upon Request	GBA	rs3115534 G/A het	KI	ENSG00000177628	IPSC0063
ID to be assigned	Available upon Request	GBA	N370S het	KI	ENSG00000177628	IPSC0063
ID to be assigned	Available upon Request	SOD1	G39A	KI	ENSG00000142168	IPSC0063
ID to be assigned	Available upon Request	SOD1	D90A	KI	ENSG00000142168	IPSC0063
IPSC0084	Available upon Request	SOD1	G93A/D90A	KI	ENSG00000142168	IPSC0063

How do you get the cells?

To request cells at the Biobank

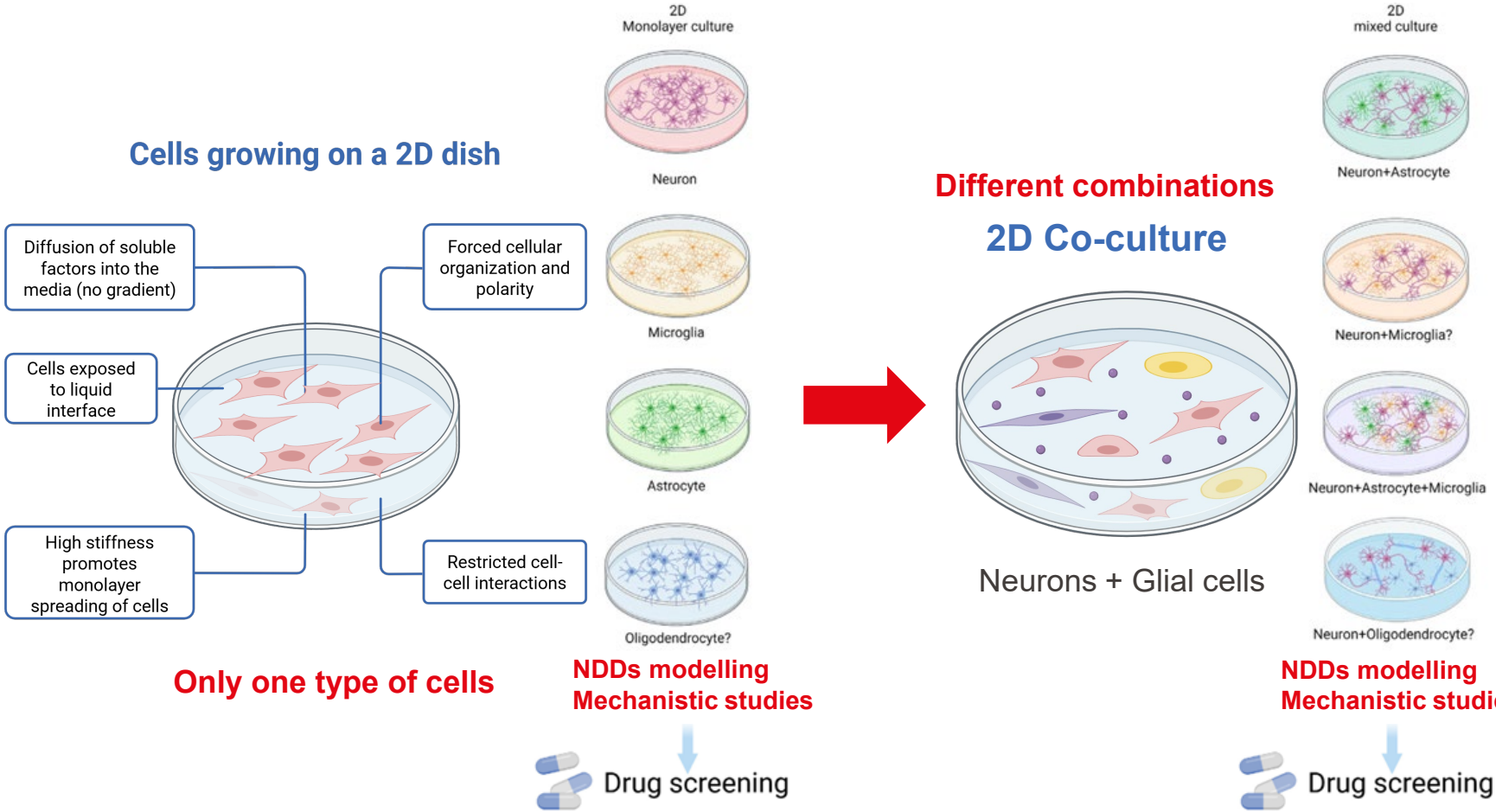
➔ 1) write a scientific proposal,

➔ 2a) evaluation by the ethical committee of the Biobank

➔ 2b) evaluation by the ethical committee of the recipient country

If 2a) and 2b) gave approval ➔ the selected cells can be shipped to the lab

IPSCs as 2D culture to model the different NDDs: ★



IPSCs as 2D culture to model the different NDDs: advantages ★

1. iPSCs preserve the patient's entire somatic genome
- All mutations, risk variants, and genetic backgrounds are kept.
- Genetically driven disease mechanisms reliably reappear in derived neurons.
- Ideal for modeling patient-specific biology.

2. iPSCs generate human, disease-relevant cell types that cannot be obtained from brain patients
- Dopaminergic neurons (PD), cortical neurons (AD), motor neurons (ALS), glia, etc.
- Direct window into human neuronal pathology.
- Essential for personalized drug testing and mechanistic studies.

3. iPSCs enable controlled, isogenic, and mechanistic experiments
- CRISPR editing: mutation corrected vs mutation introduced.
- Direct comparisons between patient lines under identical conditions.
- Clean dissection of causal pathways and drug responses.

IPSCs as 2D culture to model the different NDDs: advantages in more details (no need to learn)

Advantages of iPSCs	Relevance for Neurodegenerative Diseases
Ethical Advantage	iPSCs replace the need for embryonic stem cells → avoids ethical issues and allows unlimited access to human neural material.
Patient Specificity (genetic background)	iPSCs retain the patient's unique genetic background → essential for modeling heterogeneous diseases such as PD, AD, ALS (each patient has different mutations, modifiers, risk variants). Enables personalized disease modeling. All inherited variants and all somatic mutations present in the donor cell are preserved.
Pluripotency Cell-type–specific vulnerability (after differentiation)	iPSCs can differentiate into all relevant CNS cell types: dopaminergic, glutamatergic, GABAergic, cortical neurons; astrocytes; microglia; oligodendrocytes; endothelial cells → allows reconstruction of disease-relevant networks. iPSC-derived neurons from PD patients show PD-like vulnerabilities; AD neurons show AD-like phenotypes, etc.
Genetic Relevance (Disease-causing mutations and risk variants)	iPSCs preserve all patient-specific variants affecting neurodegeneration (e.g., LRRK2, GBA, SNCA, C9orf72, APP/PSEN1/2). Ideal for studying how genetics drives pathology and drug response.
Isogenic Controls	Using CRISPR/Cas9, mutations can be corrected or introduced → generates perfect "same patient" controls, removing genetic background noise and enabling causal interpretation of variants.
Unlimited Expansion	iPSCs self-renew indefinitely → provides stable, reproducible, large-scale batches of neurons/glia for mechanistic studies and drug screens.
Drug Screening	Enables high-throughput testing of compounds on patient-spec

IPSCs as 2D culture to model the different NDDs: Limitations ★

1. iPSCs do NOT retain the patient's original epigenetic state
- Somatic DNA methylation, histone marks, chromatin structure are erased.
- Cannot study the patient's real-life epigenetic exposures or baseline epigenome.

2. iPSCs lose the patient's biological age
- Epigenetic age resets; mitochondria and telomeres become "embryonic-like."
- Late-onset diseases (PD, AD) require artificial induction of aging to model correctly.

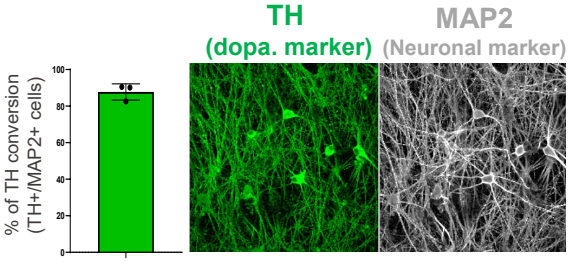
3. iPSCs do NOT retain environmental and lifestyle effects
- Toxins, diet, microbiota-driven inflammation, stress, smoking → epigenetic imprints erased.
- iPSCs reflect genetics, not environmental history.

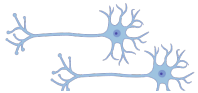
iPSCs preserve the patient's *genetic identity* but erase the patient's *biological history*. This makes them powerful for modeling genetic disease mechanisms, but insufficient to capture age or environmental contributions without further engineering.

IPSCs as 2D culture to model the different NDDs: limitations in more details (no need to learn)

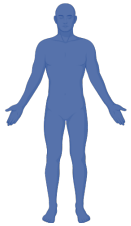
Lost after reprogrammation	Why this Is Important
Original somatic epigenetic state	**CRUCIAL:** The donor cell's DNA methylation + histone marks are erased. You cannot use iPSCs to infer a patient's original epigenetic signature.
Age-related epigenetic and cellular features	**CRITICAL:** iPSCs are "rejuvenated." Age-related changes (epigenetic clocks, chromatin aging, telomere shortening, mitochondrial aging) are wiped out. This limits modeling of late-onset diseases like PD and AD unless aging is artificially reintroduced.
Environmental/lifestyle epigenetic imprints	**IMPORTANT:** Effects of toxins, stress, smoking, microbiota-driven inflammation, etc., are not preserved. iPSCs cannot reflect the patient's lived environmental epigenome.
Somatic epimutations (but not mutations)	Epigenetic noise accumulated during life is lost—helpful for standardization but eliminates "real-life" epigenetic complexity.
Long-range somatic chromatin organization	Somatic 3D genome structure is replaced by a pluripotent architecture. This impacts gene regulation studies.
Mature mitochondrial state	iPSC mitochondria become "embryonic-like," losing many aging- or environment-related mitochondrial marks.

The induced pluripotent stem cell (iPSC) technology to model NDDs





Dopaminergic neurons
iDA

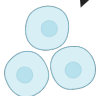


Patient/Donor

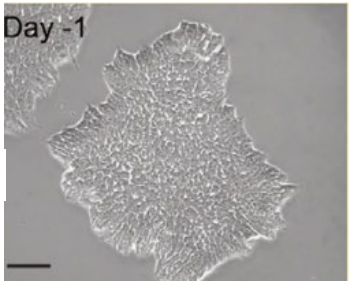
Skin Biopsy
Blood sampling

Somatic cells

Reprogramming factors
Oct4, Sox2, Klf4, c-Myc

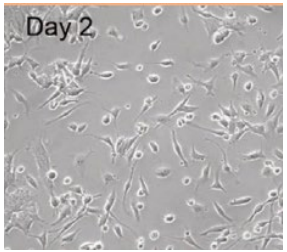


Stem cell



Neuronal Induction

NSCs

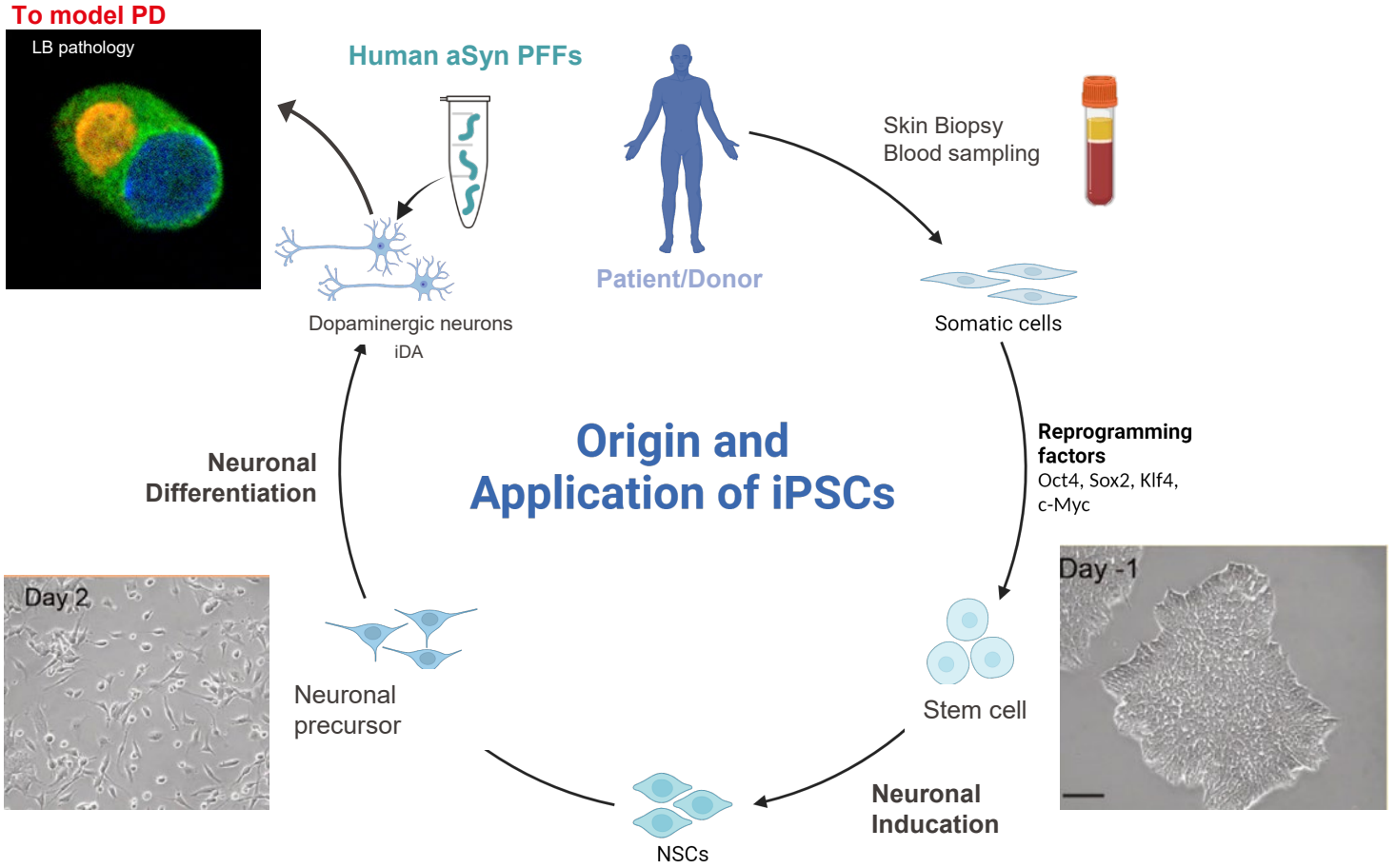


Neuronal precursor

Neuronal Differentiation

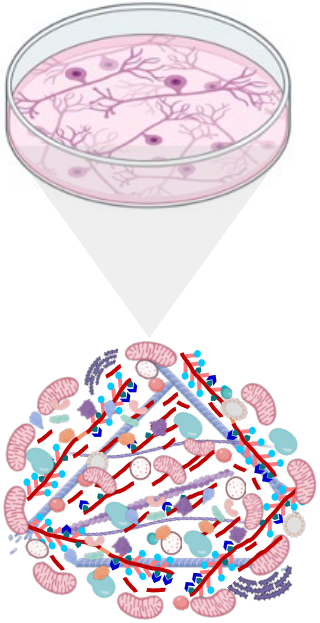
Origin and Application of iPSCs

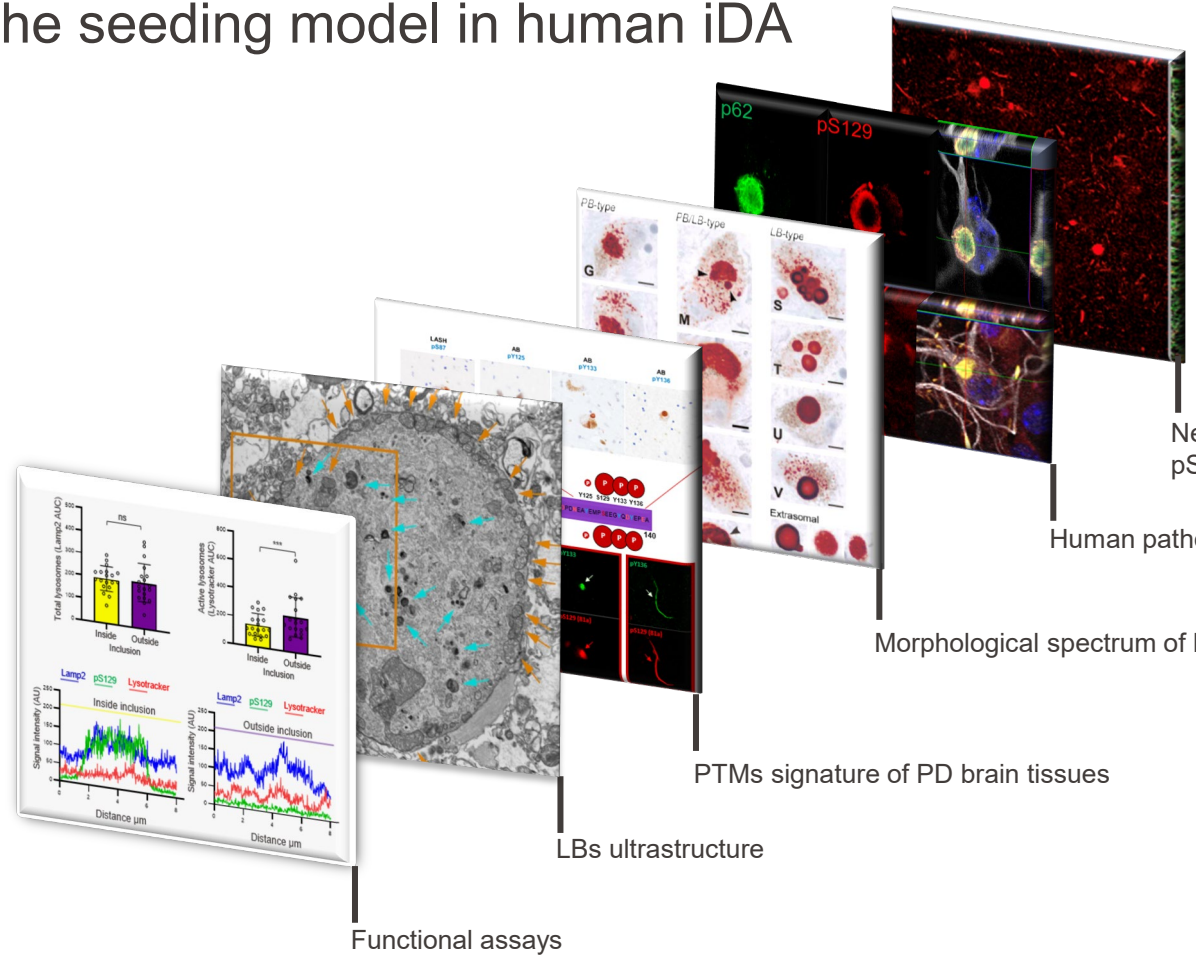
The induced pluripotent stem cell (iPSC) technology to model NDDs



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

Lewy body in a dish





Neuritic and somatic pS129 pathology

Human pathology hallmarks

Morphological spectrum of human pathology

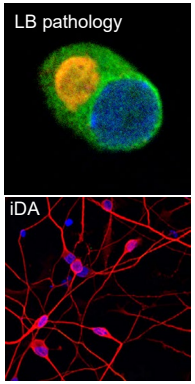
PTMs signature of PD brain tissues

LBs ultrastructure

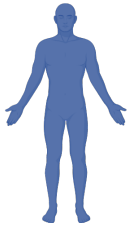
Functional assays

The induced pluripotent stem cell (iPSC) technology to model NDDs

★ To model PD



For Personalized medicine ★ Cell therapy



Patient/Donor

Phase I trial of hES cell-derived dopaminergic neurons for Parkinson's disease

https://doi.org/10.1038/s41586-025-08845-y
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Accepted: 26 February 2025

V. Tabar[1,2,3]✉, H. Sarva[4], A. M. Lozano[5,6], A. Fasano[6,7,8], S. K. Kalia[5,6], K. K. H. Yu[1], C. Brennan[1], Y. Ma[9,10], S. Peng[9], D. Eidelberg[9,10], M. Tomishima[11], S. Irion[11], W. Stemple[11], N. Abid[11], A. Lampron[11], L. Studer[2,12,14] & C. Henchcliffe[13,14]

Phase I/II trial of iPS-cell-derived dopaminergic cells for Parkinson's disease

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Accepted: 24 January 2025
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Nobukatsu Sawamoto[1,8], Daisuke Doi[2,8], Etsuro Nakanishi[1,8], Masanori Sawamura[1,8], Takayuki Kikuchi[3], Hodaka Yamakado[1], Yosuke Taruno[1], Atsushi Shima[1], Yasutaka Fushimi[4], Tomohisa Okada[4], Tetsuhiro Kikuchi[2], Asuka Morizane[2], Satoe Hiramatsu[2], Takayuki Anazawa[5], Takero Shindo[6], Kentaro Ueno[7], Satoshi Morita[7], Yoshiki Arakawa[3], Yuji Nakamoto[4], Susumu Miyamoto[3], Ryosuke Takahashi[1]✉ & Jun Takahashi[2]✉

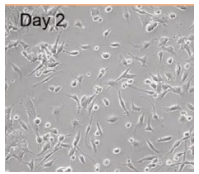
Phase 1/2a clinical trial of hESC-derived dopamine progenitors in Parkinson's disease

Jin Woo Chang,[1,11] Han Kyu Na,[2,11] Kyung Won Chang,[3,11] Chan Wook Park,[2,4,11] Do-Hun Kim,[4,5] Sanghyun Park,[4] Chul-Yong Park,[4,5] Jang Hyeon Eom,[5] Seung Taek Nam,[5] Ki-Sang Jo,[5] Mi-Young Jo,[5] Sung Kyoung Choi,[5] Hye-Jin Hur,[5] Sarang Kim,[5] Minseok Kim,[6] Dae-Sung Kim,[7] Dong-Youn Hwang,[8] Myoung Soo Kim,[9] Inkyung Jung,[6] Jongwan Kim,[5] Myung Soo Cho,[5] Phil Hyu Lee,[2,*] and Dong-Wook Kim[4,5,10,12,*]

Origin and Application of i

Dopaminergic neurons iDA

Neuronal Differentiation



Neuronal precursor

NSCs

Neur Indu

BlueRock THERAPEUTICS × BAYER

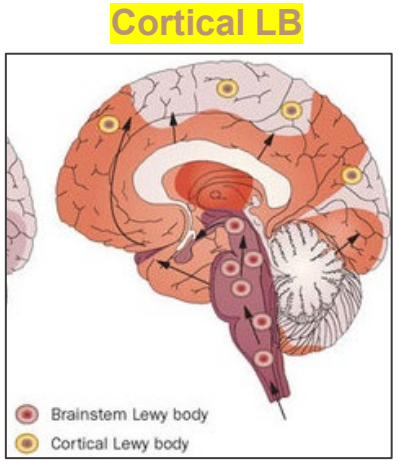
Bemdaneprocel (BRT-DA01)
Phase I - 12 patients

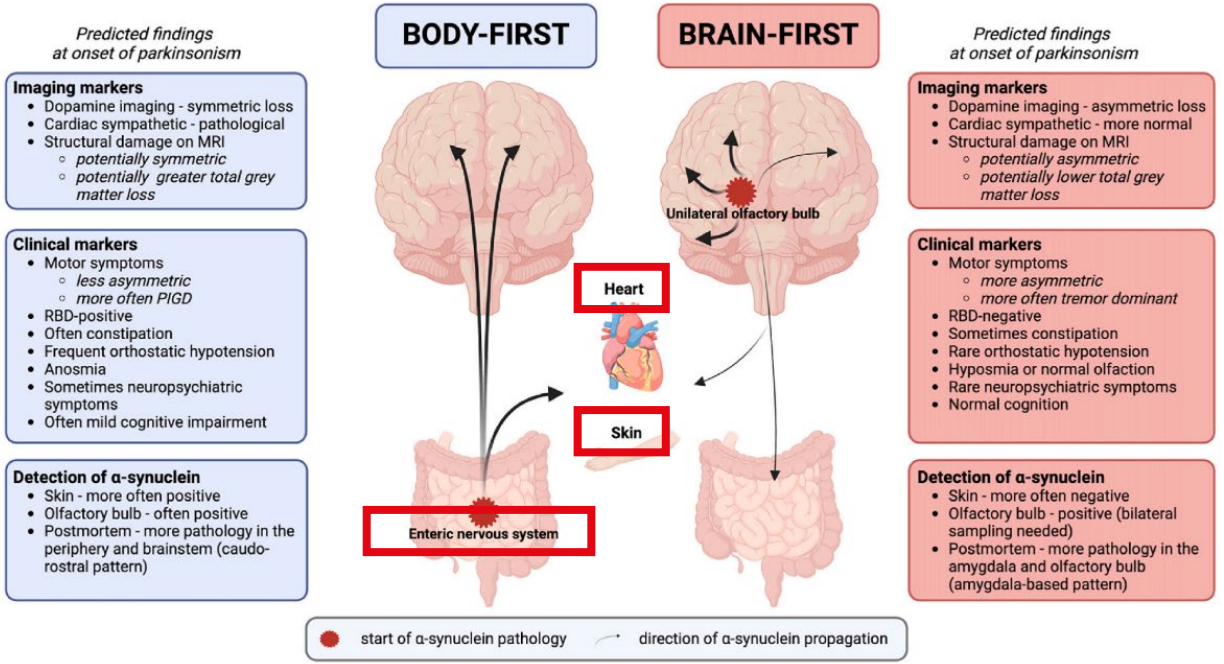
Update on STEM-PD clinical trial – stem cell-based transplant for Parkinson's disease

LUND UNIVERSITY

Phase I - 8 patients

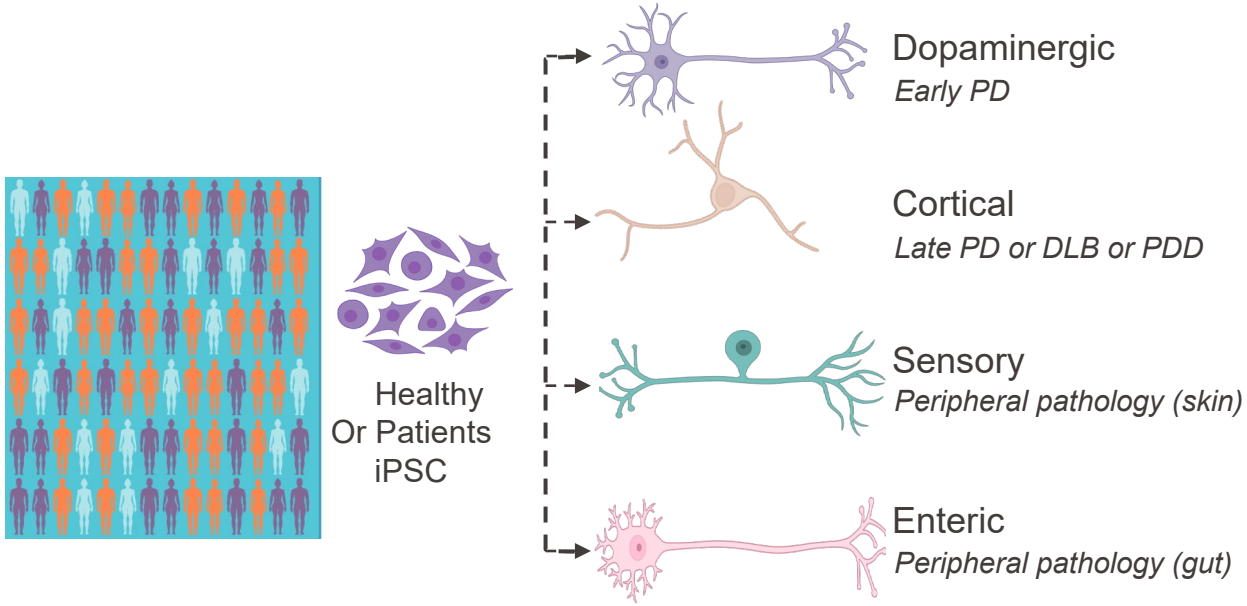
What other neurons are relevant in PD modelling ?





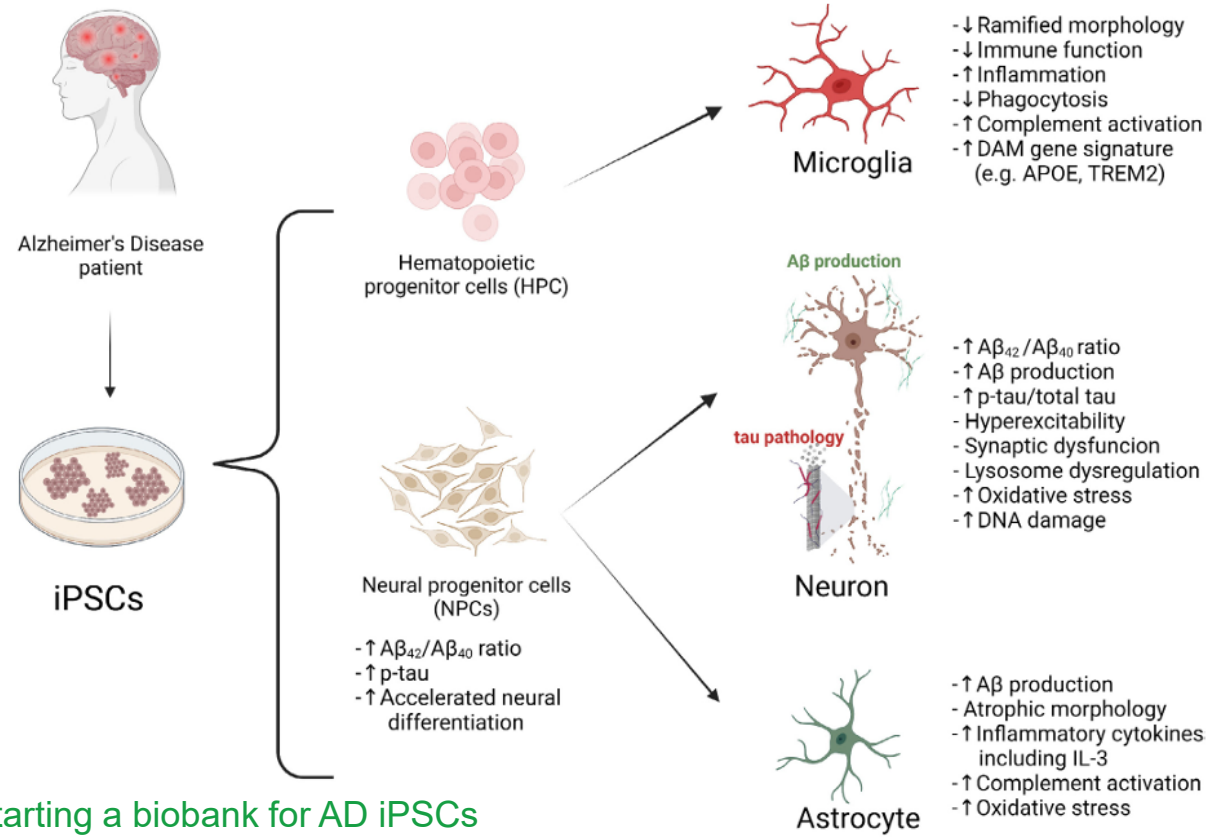
iPSCs are pluripotent cells ➔ they can be differentiated in any relevant cells where PD pathology is observed in human tissues

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



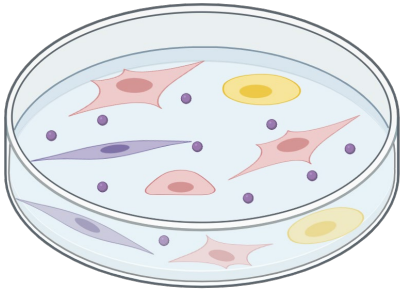
- **They carry the patient's genetic identity**
  Keep the person's **genetic** profile ➔ the most faithful model of the disease.
- **They make research closer to patients**
  Allow study of disease mechanisms directly in **human neurons** and improve prediction of clinical drug responses.
- **They open the door to personalized medicine**
  Comparing cells from multiple patients helps identify which patients respond best to specific treatments.

IPSCs to model the different NDDs: AD



CHUV Is starting a biobank for AD iPSCs

Limitations of the **2D cultures** to model the different NDDs: ★



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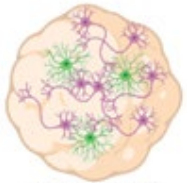
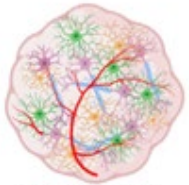
Use of iPSCs as 2D culture	Limitations
Biological Maturity	Immature, fetal-like neurons; limited long-term survival (2-3 months)
Architecture	**No 3D structure**; poor spatial organization; simplified network formation
Cell–Cell Interactions	Weak (if no co-culture) and immune–neuron interactions
Aging	Requires artificial aging methods; poor modelling of late-onset degeneration
Physiological Relevance	Limited synaptic complexity; reduced metabolic + electrophysiological realism
Technical Variability	Sensitive to culture conditions; inter-line variability
Disease Modeling Limitations	Protein aggregation and chronic toxicity hard to recapitulate in 2D
Drug Testing Limitations	May not predict in vivo or organoid responses

Organoids to model the different NDDs:

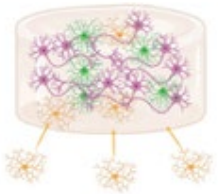
3D



Brain Organoid without microglia & vasculature



Brain Organoid with all brain cell types and vasculature ?

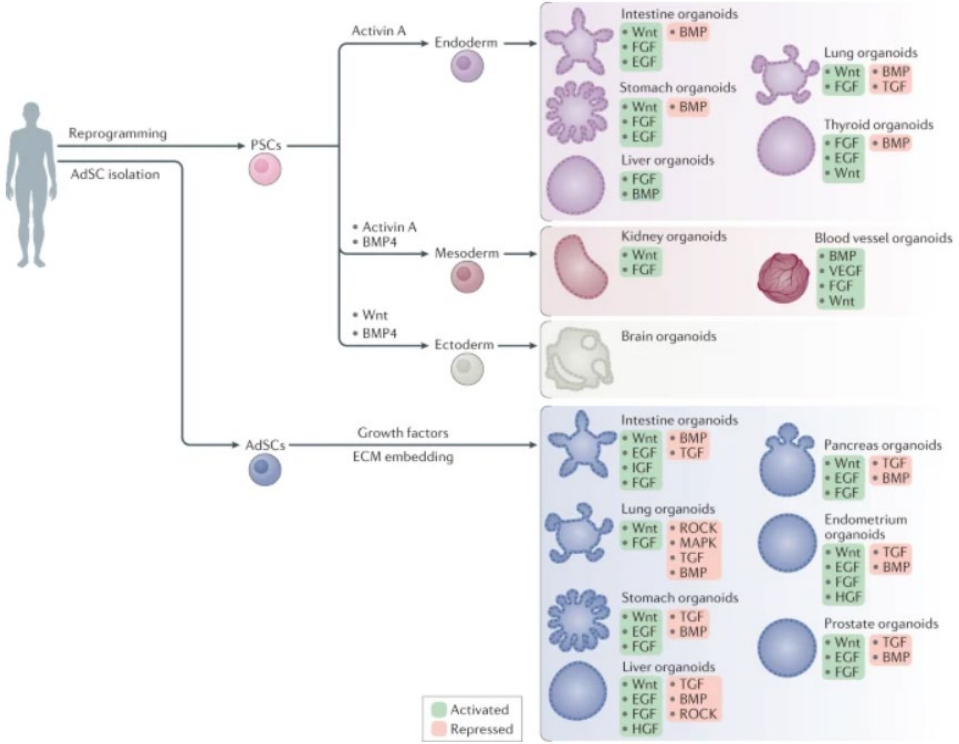


Mixed 3D culture

NDDs modelling
Mechanistic studies

Drug screening

Fig. 2: Process for the establishment of human PSC-derived and AdSC-derived organoids.



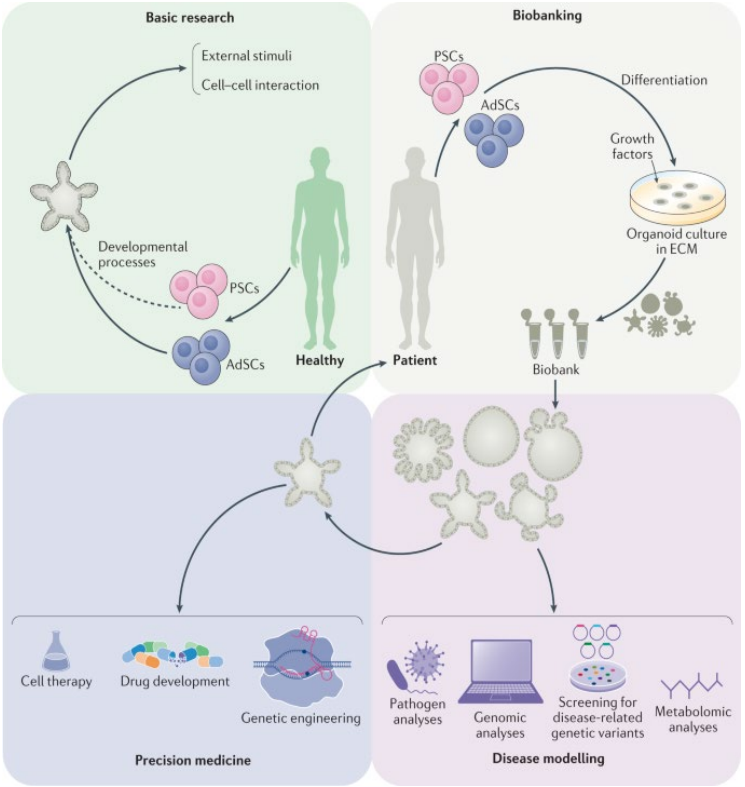
https://www.nature.com/articles/s41580-020-0259-3

Advantages and potential applications for organoids: ★

1. Organoids provide a 3D, multicellular human brain-like environment
•Neurons, astrocytes, oligodendrocyte lineage cells, sometimes microglia.
•Enable modeling of cell–cell interactions driving neurodegeneration.
•More physiologically relevant than 2D neuronal cultures.

2. Organoids capture human-specific regional and network features
•Can generate cortical, midbrain, hippocampal, or spinal organoids.
•Allow study of selective vulnerability (e.g., dopaminergic neurons in PD, cortical layers in AD).
•Display early network activity and synaptic dysfunction relevant to NDDs.

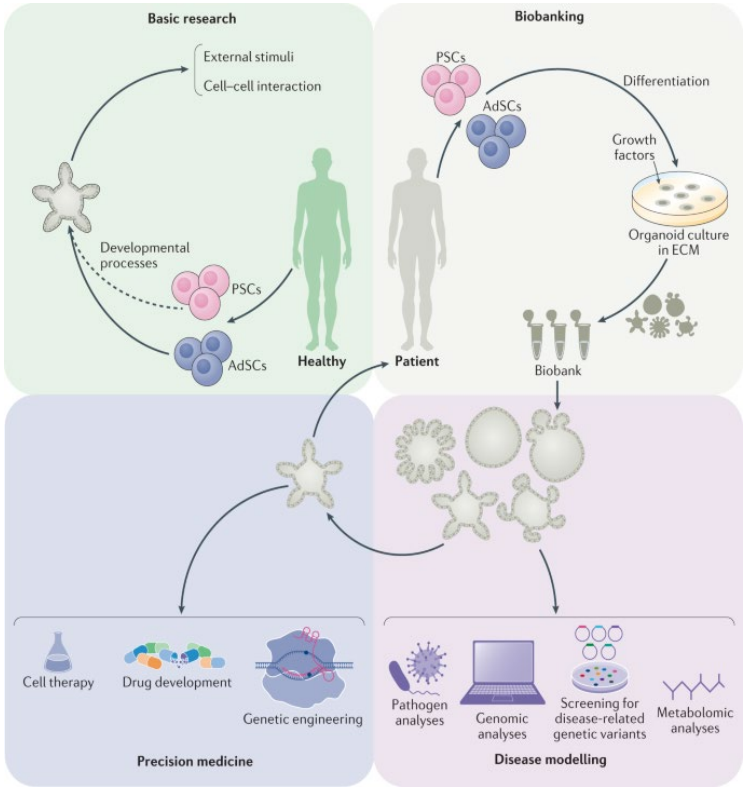
3. Organoids enable long-term modeling of disease progression
•Support months-long cultures.
•Useful for studying progressive phenotypes such as protein aggregation (aSyn, tau, Aβ), synaptic decay, and chronic metabolic stress.
•Can be derived from patient-specific iPSCs → **personalized organoids**.



https://www.nature.com/articles/s41580-020-0259-3

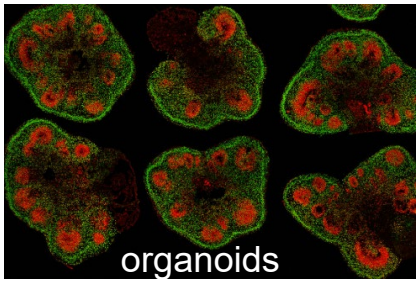
Advantages and potential applications for organoids: (more details – not to learn)

Criteria	Advantages for Neurodegenerative Disease Research
3D Architecture	**Recapitulate spatial organization, cell layering, and tissue** microdomains relevant for PD (midbrain), AD (cortex, hippocampus), or ALS (spinal-like organoids).
Cellular Diversity	Contain neurons + astrocytes + oligodendrocyte lineage + sometimes microglia, allowing study of **cell–cell interactions** driving neurodegeneration.
Developmental & Regional Patterning	**Region-specific organoids** (midbrain, cortical, hippocampal) allow modeling of **selective vulnerability** (e.g., dopaminergic neurons in PD, cortical neurons in AD).
Network Formation	Generate **spontaneous activity** and network-level dysfunction similar to early synaptic deficits, useful for studying early AD synaptic failure or PD oscillation changes.
Long-Term Culture	**Can be grown for months** → useful for studying progression of amyloid/tau accumulation, aSyn propagation, or chronic metabolic stress.
Disease Modeling in a Physiological-Like Context	More realistic **microenvironment** reveals phenotypes missed in 2D cultures: protein spreading, inflammation, synaptic network deficits.
Genetic Relevance	Patient-derived iPSC organoids mirror patient-specific genetic backgrounds → personalized disease models for PD, AD, ALS.
Scalability & Flexibility	Region-specific organoids allow comparative studies: cortical (AD), midbrain (PD), spinal (ALS), striatal (HD).
Protein Aggregation Modeling	Organoids can show aSyn, tau, amyloid, or TDP-43 aggregation in a **tissue-like context (Spreading/transmission)**
Pathway Interaction Modeling	Useful for investigating interactions between neurons, glia, and extracellular matrix relevant for inflammation and neurodegeneration.



https://www.nature.com/articles/s41580-020-0259-3

Limitation of the use of organoids in modelling NDDs★



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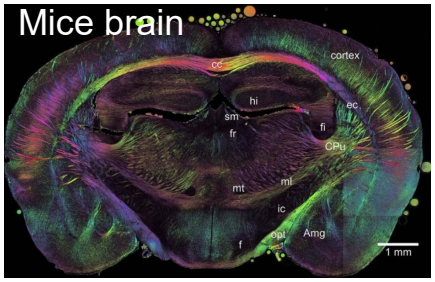
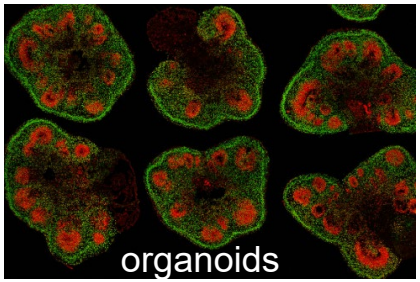


1. Organoids resemble fetal tissue, not aged adult brain
- Cannot naturally model late-onset diseases (PD, AD, ALS) without adding artificial aging.
- Age-dependent phenotypes and epigenetic marks are missing.

2. Lack of vasculature and full immune system
- Limited oxygen/nutrient diffusion → necrotic cores, incomplete maturation.
- Neuroinflammation and neurovascular interactions are only partially represented.

3. High variability and limited assay compatibility
- Batch-to-batch differences reduce reproducibility.
- Thick 3D structure complicates drug penetration, imaging, electrophysiology, and high-throughput screening.
- Protocol differences across labs lead to inconsistent phenotypes.

Limitation of the use of organoids in modelling NDDs (in details – not to learn)



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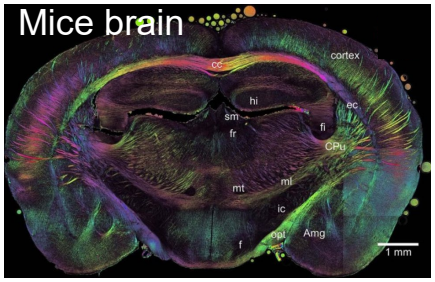
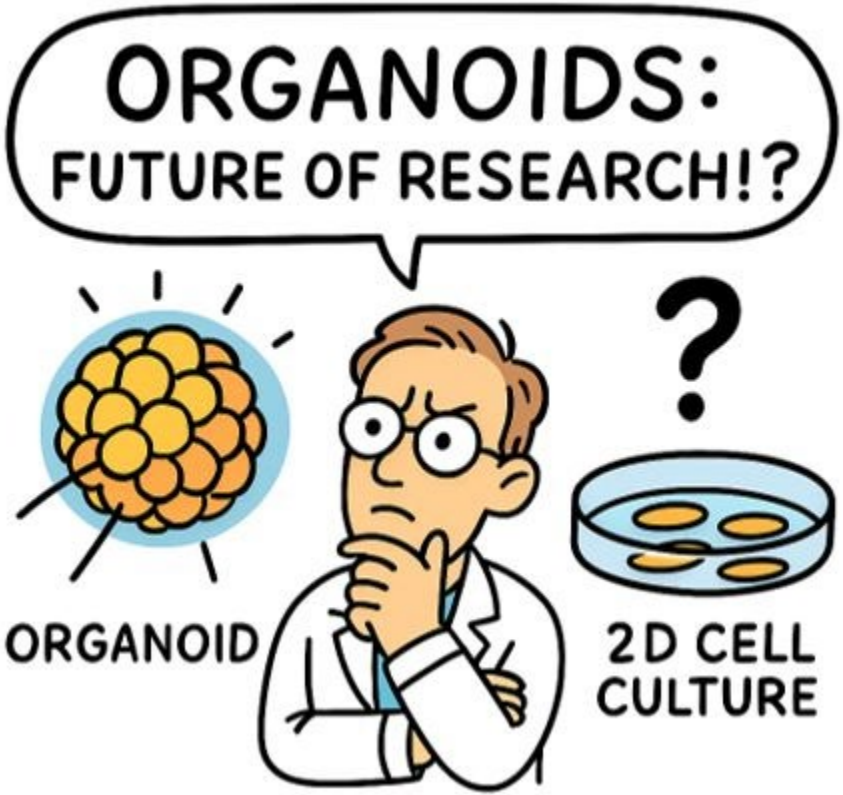


Aspect	Disadvantages / Limitations
3D Architecture	Lack full adult brain architecture; no vascular system; limited nutrient and oxygen diffusion → risk of necrotic cores and incomplete maturation.
Cellular Diversity	Microglia often incomplete or absent; immune interactions only partially modeled; substantial heterogeneity between batches.
Developmental & Regional Patterning	Organoids resemble **fetal**, not adult or aged tissue → poor modeling of late-onset diseases (PD, AD, ALS) unless aging is artificially induced.
Network Formation	Neural networks remain immature compared to adult brain; lack long-range connectivity and realistic input–output circuits.
Human-Specific Features	Cannot fully reproduce complex human circuits, behavioral-level integration, or long-term systemic interactions.
Long-Term Culture	Survival limited beyond certain timepoints; tendency to form necrotic centers; culture instability increases with duration; costly and time-intensive.
Modeling in a Physiological-Like Context	Developmental trajectory is difficult to control; high variability between organoids decreases reproducibility; phenotypes may differ across batches or labs.
Genetic Relevance	Organoids do **not** retain patient age, environment, or epigenetic history — only genetics-driven phenotypes re-emerge.
Scalability & Flexibility	Scalability improving but still limited; protocols often labor-intensive; batch effects complicate high-throughput applications; high variability across laboratories.
Protein Aggregation Modeling	Pathological aggregation (aSyn, tau, TDP-43) often requires added stressors or overexpression; timelines may not accurately reflect human disease progression.
Pathway Interaction Modeling	Missing vascular, hormonal, and systemic immune signals crucial for neurodegenerative processes → incomplete modeling of neuroinflammation and neurovascular interactions.
Mechanistic Study Limits	Deep-tissue imaging and electrophysiology are difficult in thick 3D structures; limited access for CRISPR editing, perturbations, and single-cell manipulation.
Assay Compatibility Issues	3D structure is poorly compatible with many high-throughput screens; drug penetration is uneven; quantification is less precise than in 2D cultures.

Limitations of the Organoids to model the different NDDs:



Organoids and 2D cell cultures are complementary to model NDDs ★

Choose a 2D model for:	Choose a 3D model for:
High-throughput screening experiments, e.g., screening assays with up to 384/1536 wells. Here, 2D cultures are more cost-effective and scalable than 3D formats.	Disease modeling that requires microtissue structures , e.g., when studying cell-cell morphology and cell-matrix interactions.
Mechanistic pathway studies requiring uniform conditions, e.g., when testing a kinase inhibitor. In a 2D setup, all cells will (theoretically) experience the same conditions (e.g., drug concentration, nutrient access and oxygenation), while in a 3D setup, cells in the center may experience different conditions than cells on the outer surfaces.	Physiologically-relevant testing of lead drug candidates, e.g., hepatocytes for accurate CYP metabolism studies, since enzyme activity tends to decline within days in cells grown in 2D cultures. Any study that requires greater metabolic complexity since enzymatic activity may decline faster in 2D than in 3D culture formats.
Large repetitive studies that need fast data turnaround. Many standardized protocols exist for 2D cultures which may increase speed and reproducibility, e.g., during screening experiments.	Situations where different conditions (nutrients, oxygen along a gradient) are required in different parts of the tissue to mimic the *in vivo* situation, e.g., in tumors.
Studies involving 1-3 cell types, such as cytotoxicity testing, basic co-culture experiments, and myelination studies using phenotypic visualization, e.g., culturing neurons and oligodendrocyte precursor cells together, with or without astrocytes, which are much easier to analyze in 2D formats.	Experiments that require long-term culture stability as cells in 3D tissues tend to retain their tissue-specific functions for a longer period (typically 4-6 weeks or longer) than their 2D counterparts.

https://www.tempobioscience.com/2d-vs-3d-cell-culture-choosing-the-right-model-by-tempo-bioscience/

Therapeutic strategies against synucleinopathies

See exercises in the Moodle

“**Personalized/precision medicine:**”

Any questions ? Or Thoughts ?