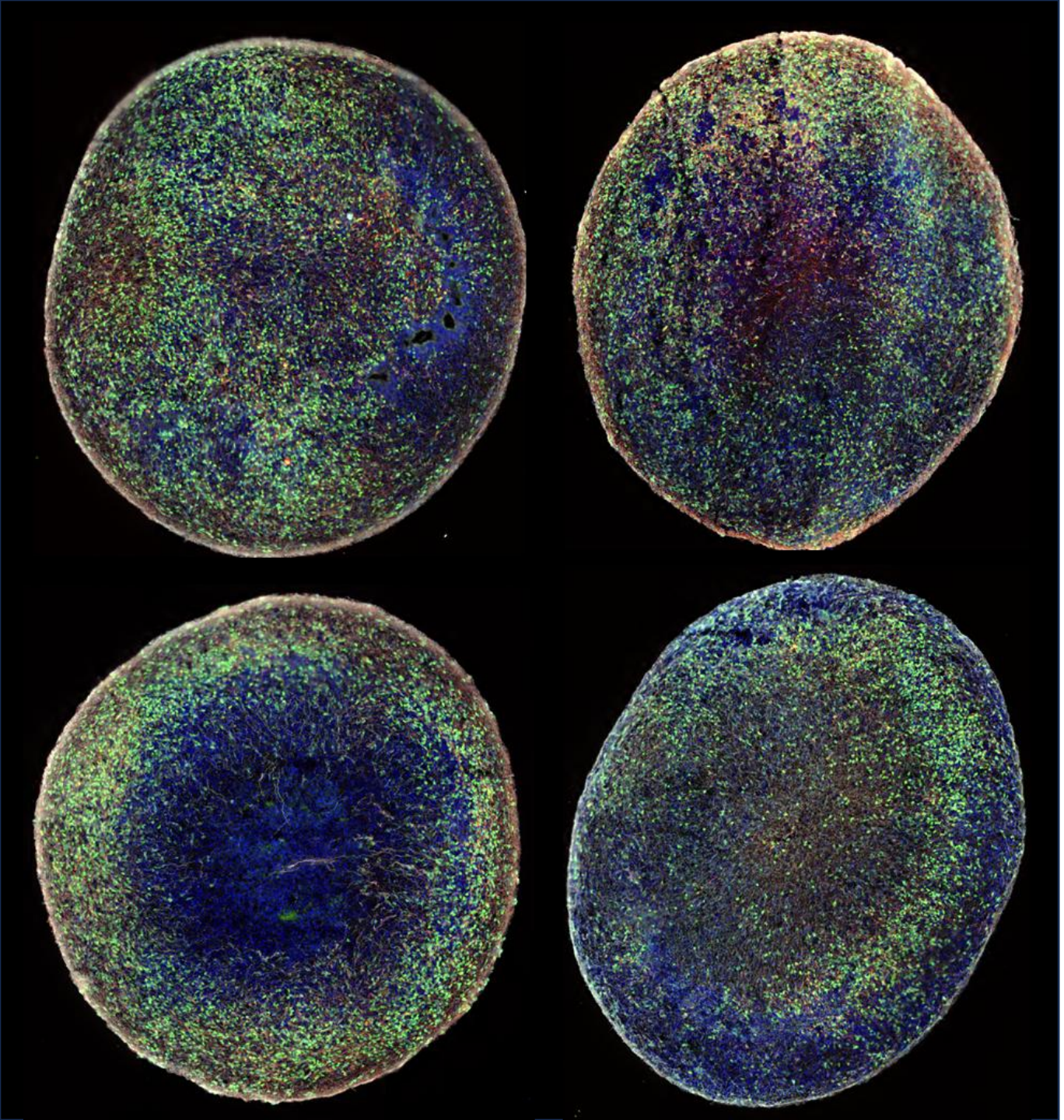
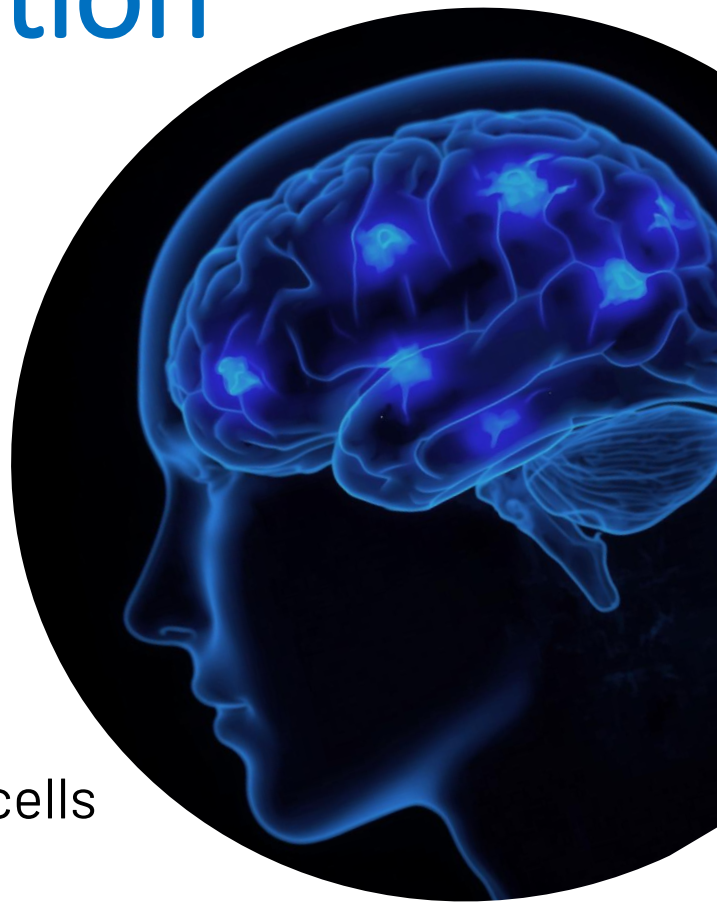


Brain Organoids: A human cell model to develop drugs for Frontotemporal dementia (FTD)-tau

Sally Temple, PhD
Neural Stem Cell Institute
sallytemple@neuralsci.org

Dec 2025

The Unmet Need: Neurodegeneration



Millions of People Affected Worldwide

- Alzheimer's Disease: 6.7M U.S. | 50M global
- Parkinson's Disease: 1M U.S. | 10M global
- Huntington's Disease: 30K U.S. | 200K global

Current Therapies Fall Short

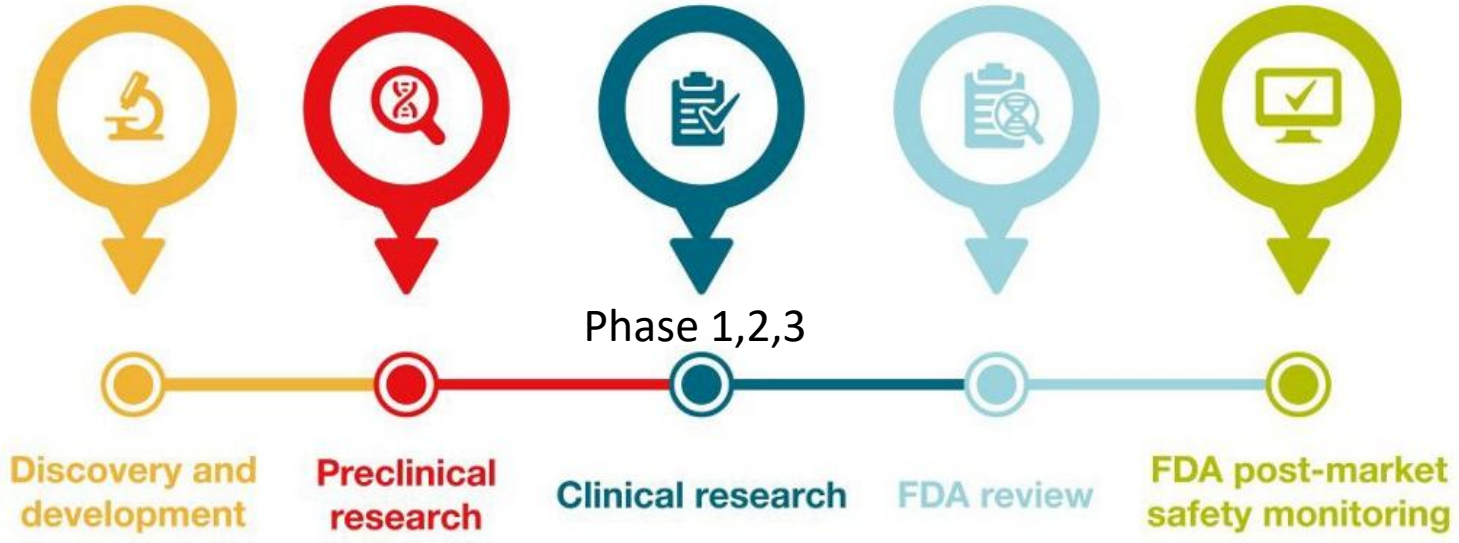
- Intracellular aggregation drives neuronal death
- Existing drugs do not target toxic proteins inside cells

Urgent Need for Neuroprotective Interventions

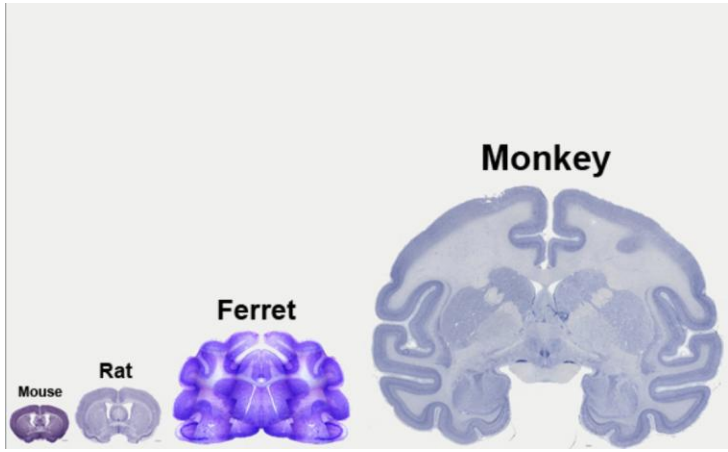
- Eliminate toxic proteins within neurons
- Preserve neuronal function and prevent progression

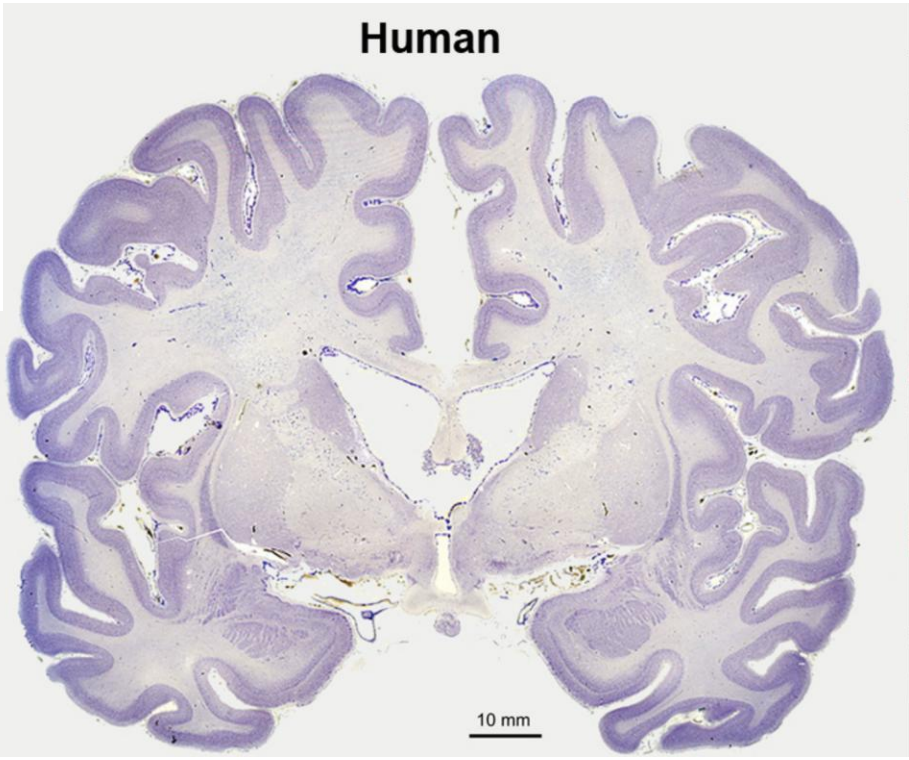
How drugs are developed

Need human cell models:
Congress: FDA Modernization Act 2.0, Dec 2022
FDA and NIH changes to use and develop non-animal models

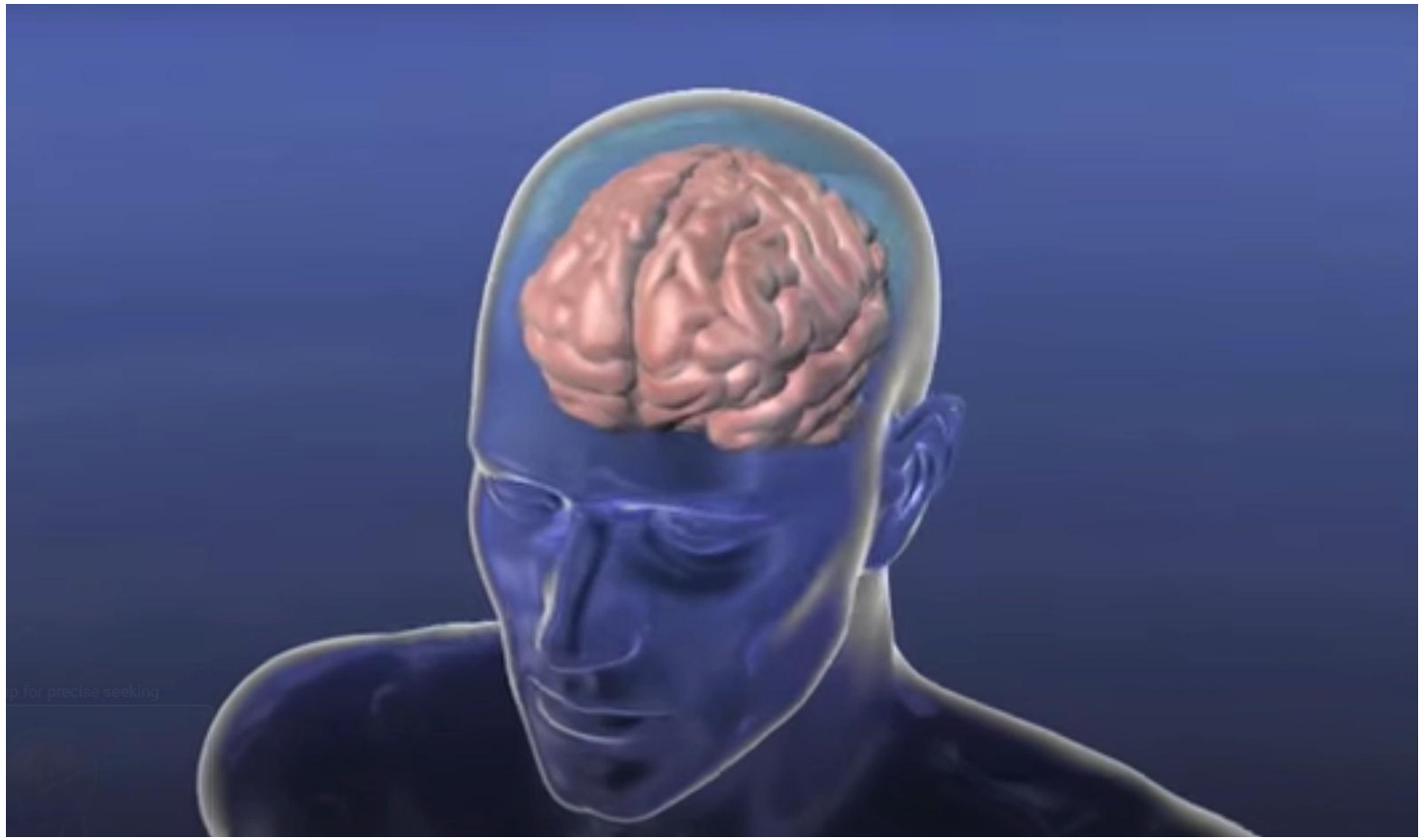


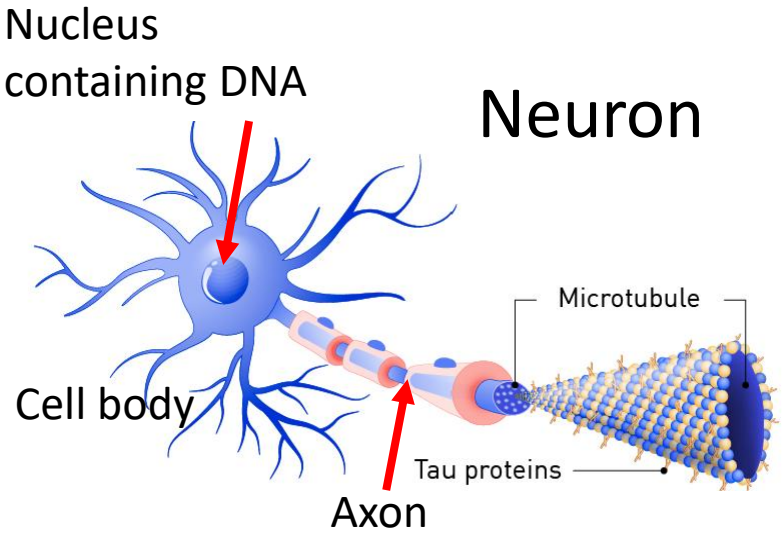
c. 2000 genes human-specific patterns

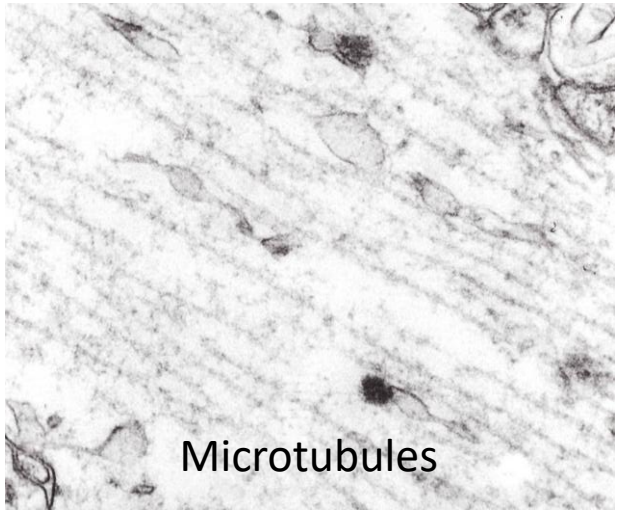




What is tau protein?

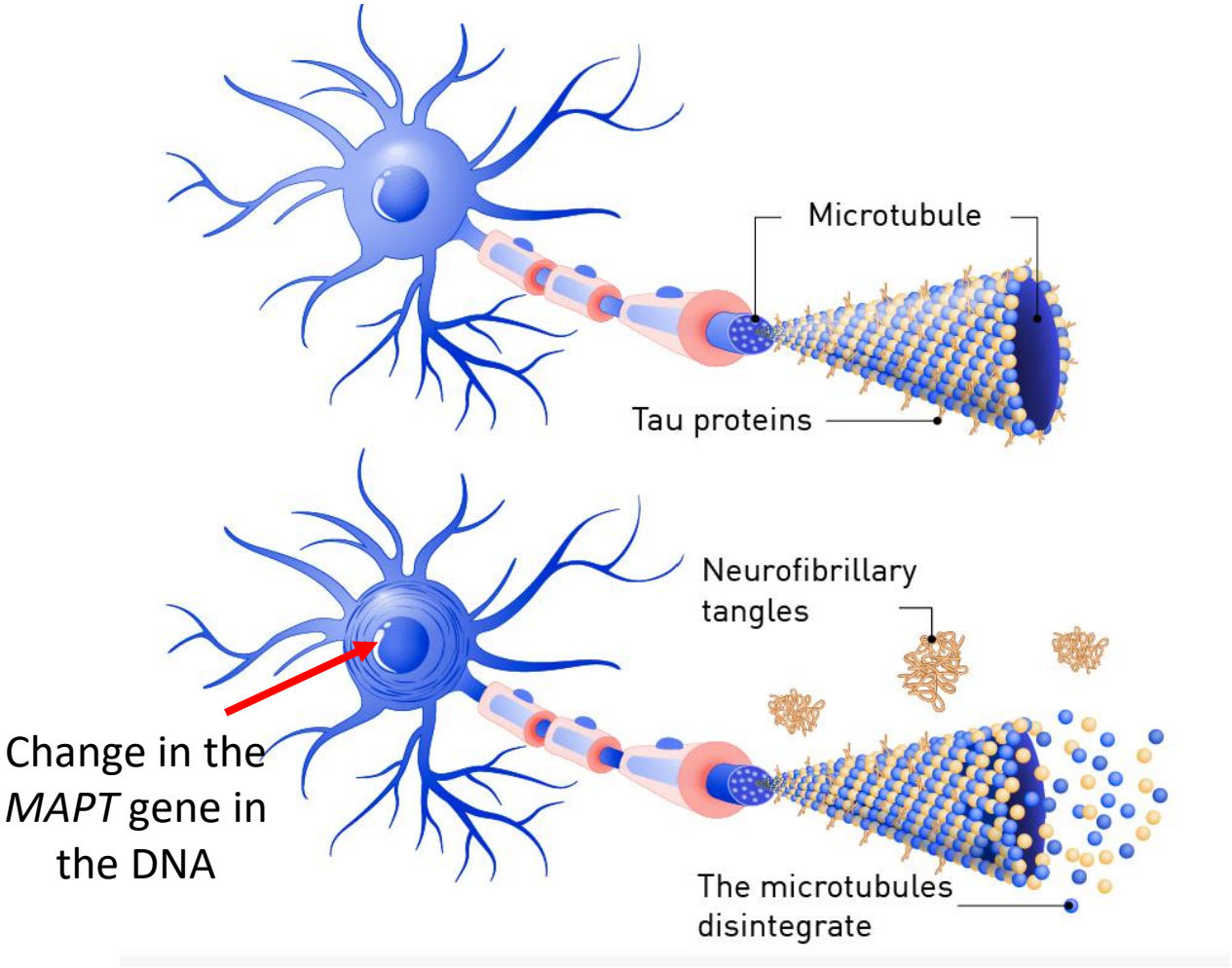






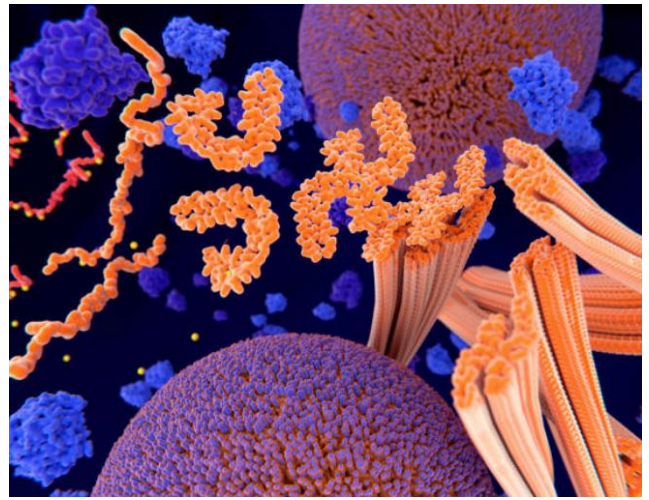
A key molecule in **Neurons**, the excitable cells in the brain that carry signals for all nervous system functions

Changes in the MAPT gene that encodes tau leads to tau protein aggregation



Tau aggregation occurs in FTD, PSP, CBD, Alzheimer's disease: "Tauopathies"

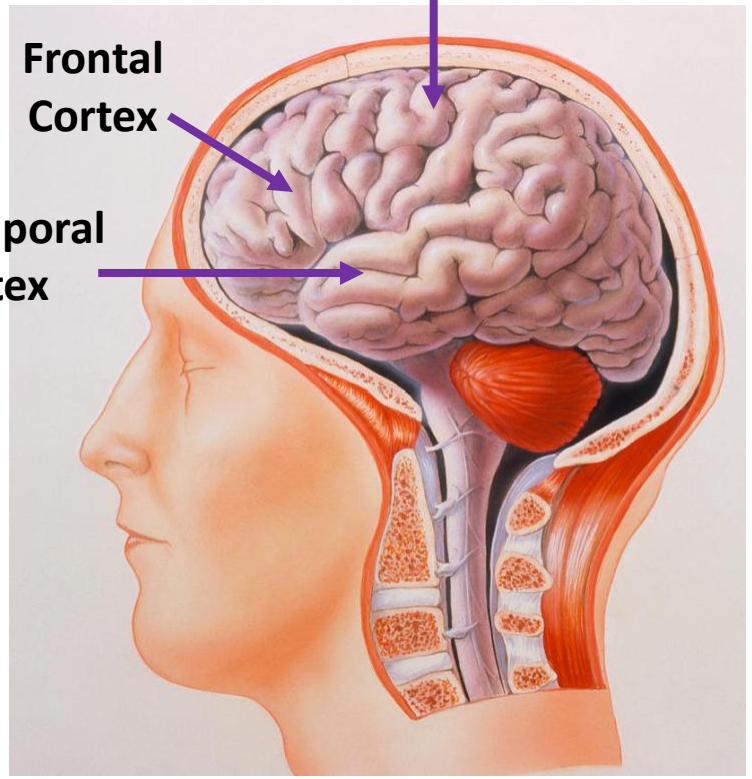
Tau protein aggregates into 'tangles'



Frontotemporal dementia (FTD) due to build up of toxic tau protein

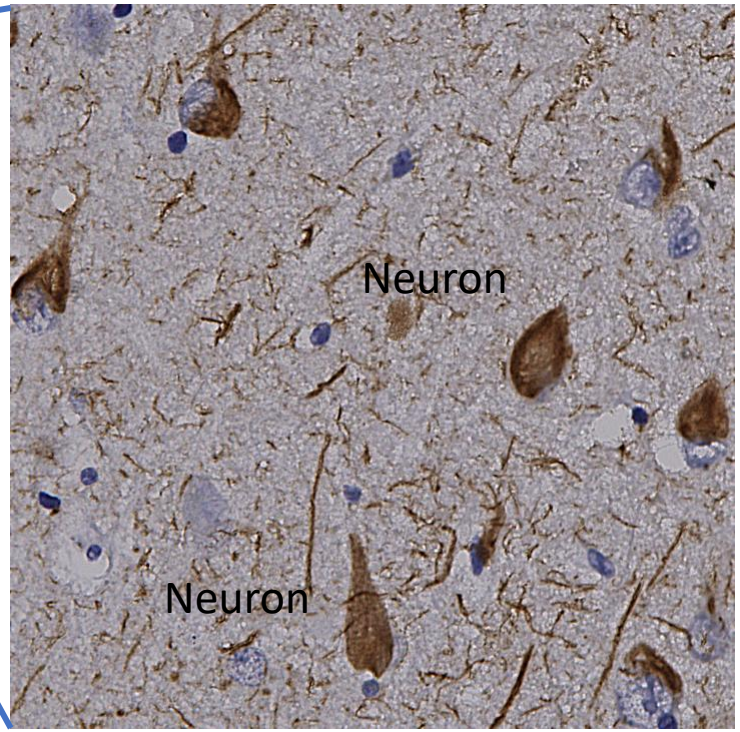
Brain

Cerebral Cortex



Brain Section
1000th inch thick

Neurons containing aggregated tau



High Magnification

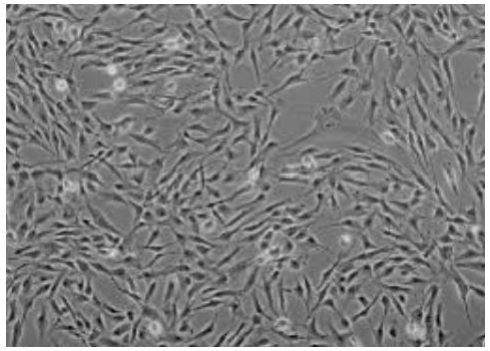
- *What is the time course of changes leading to neurodegeneration?*
- *What is the disease mechanism?*
- *Can we stop or even reverse it?*

Our goal: to cure FTD

What if we could create a model that would help us understand the disease better and identify new drugs?

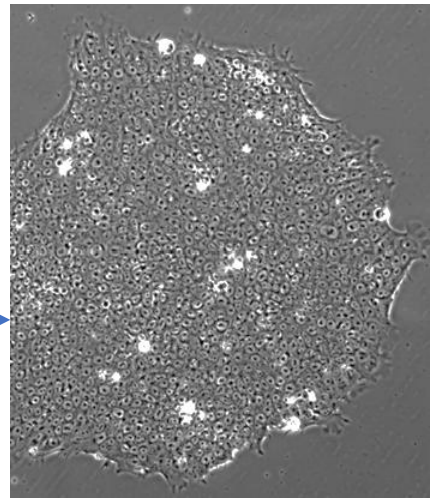
Human Brain Organoids

Shinya Yamanaka: Invented Human induced pluripotent stem cells (iPSCs)



Skin cells

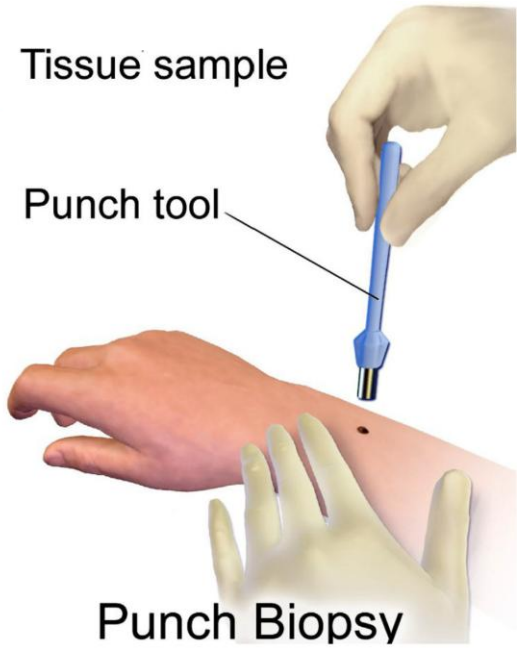
Insert 4 genes



Induced pluripotent stem cells (iPSCs)

- Ethically sourced stem cells
- Can generate all tissues of the body

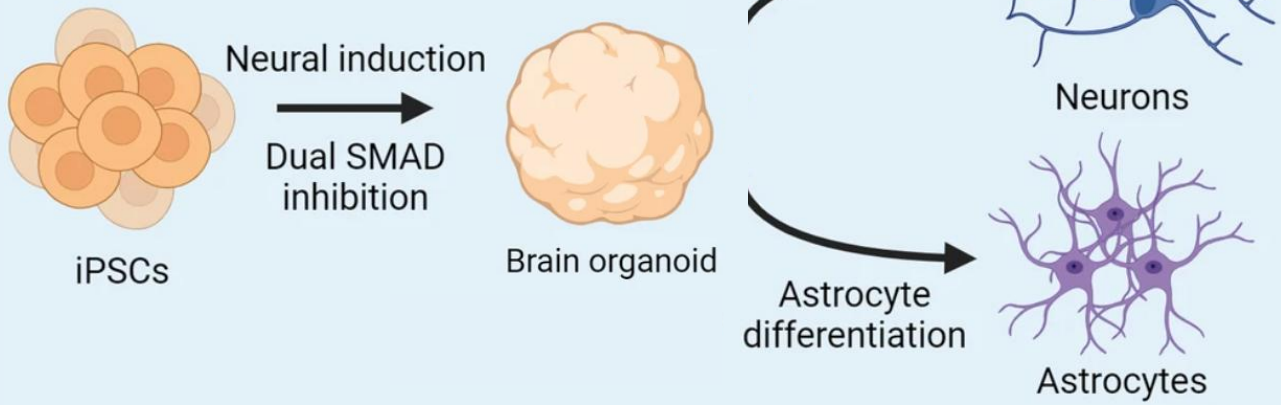
1. Collect skin or blood sample from patient



Skin cells →

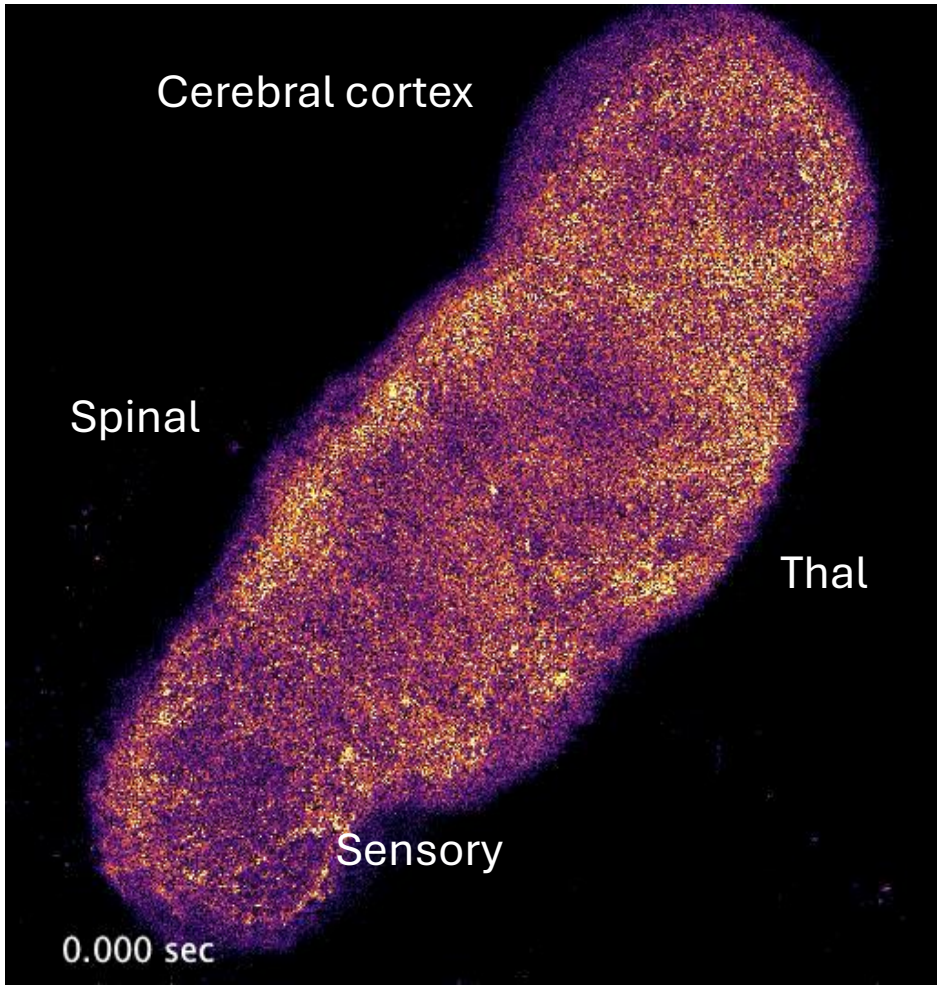
2. Reprogram the skin cells into induced pluripotent stem cells

3. Differentiate the iPSCs into brain organoids



2-3 mm in diameter
Contain the same brain cells affected in FTD

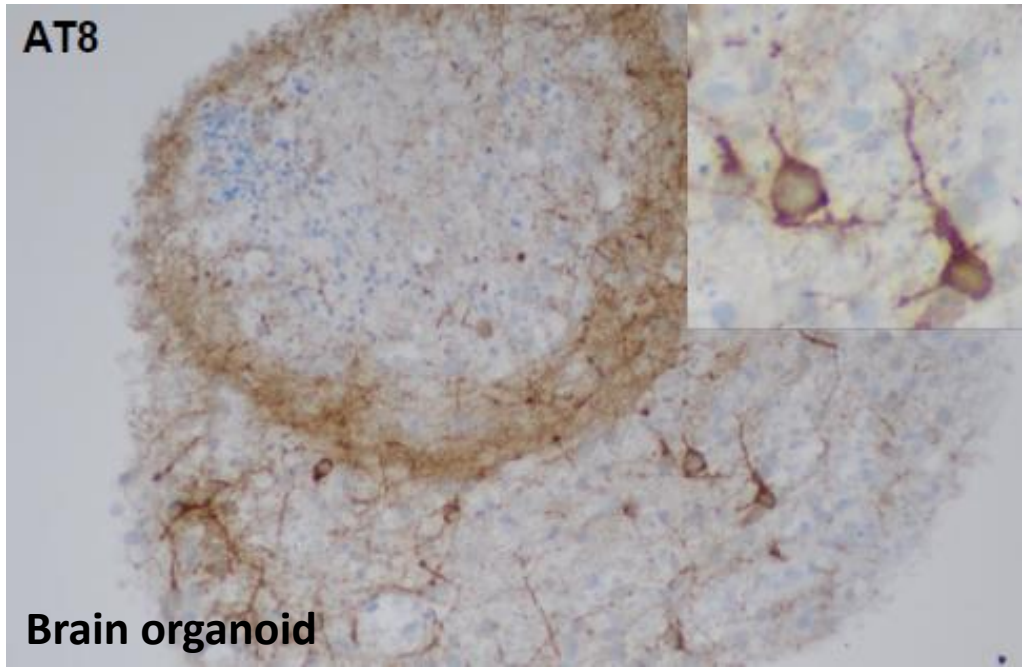
3D organoids have electrical activity like the brain

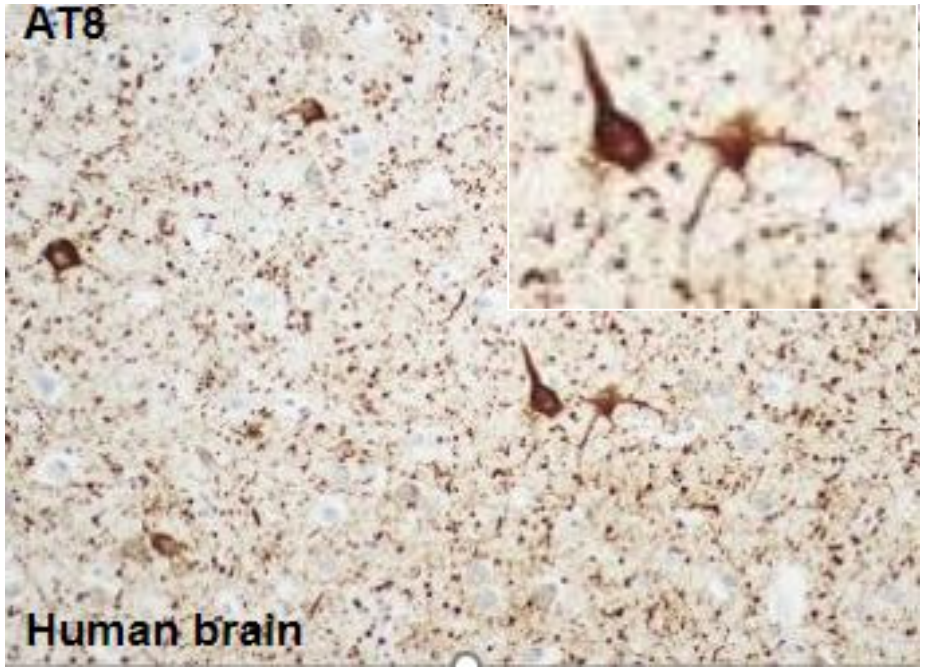


Sergiu Pasca, Stanford University

MAPT mutation organoids show critical features of disease

1. Build up of abnormal tau in organoids as seen in the brain

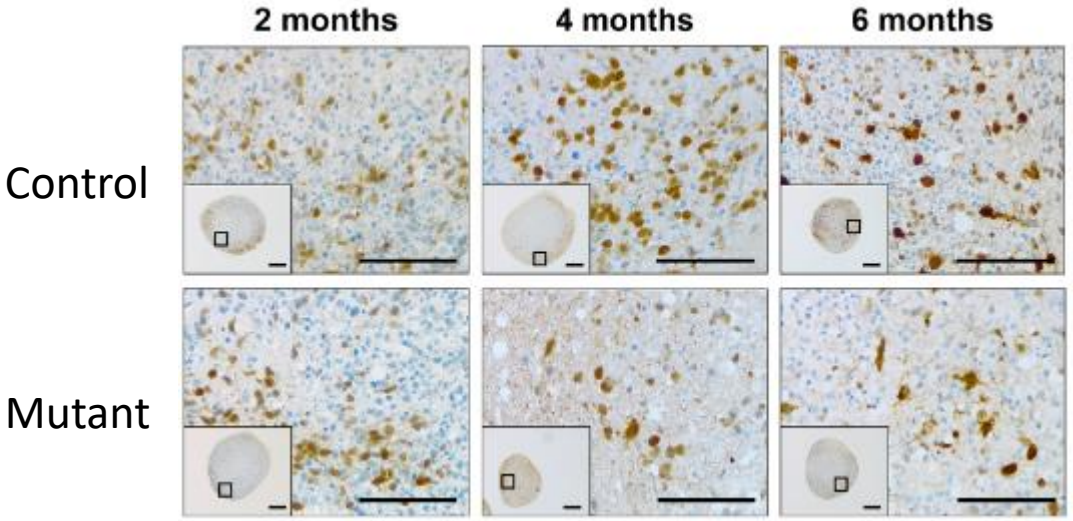


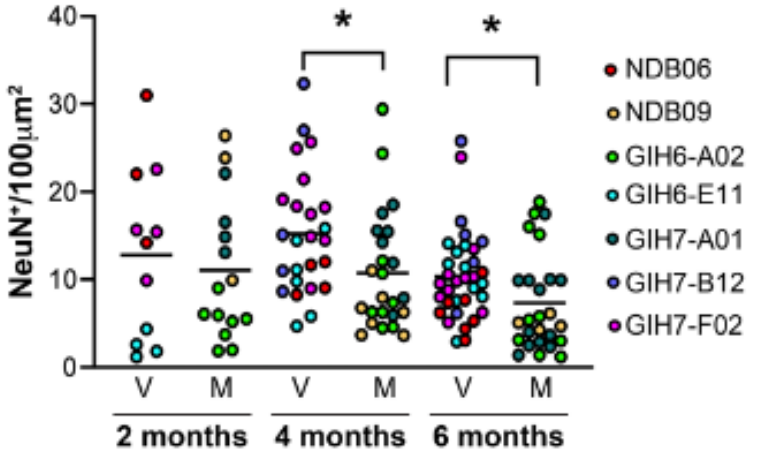


Drs. Kristen Whitney, John Crary, Mt Sinai Medical School, NY

2. *MAPT* Mutation Organoids show Death of Neurons over time, as seen in the brain

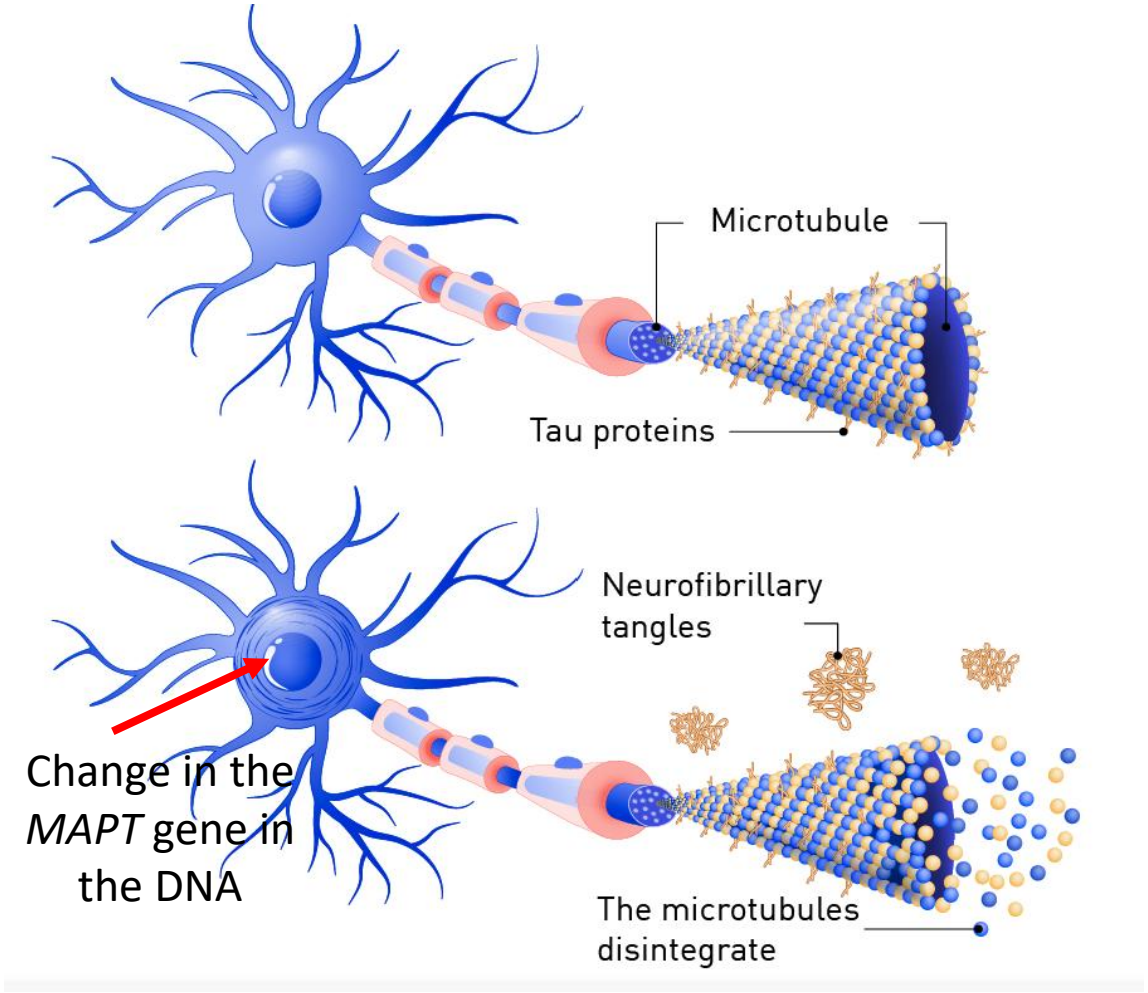
Neuronal (NeuN) staining



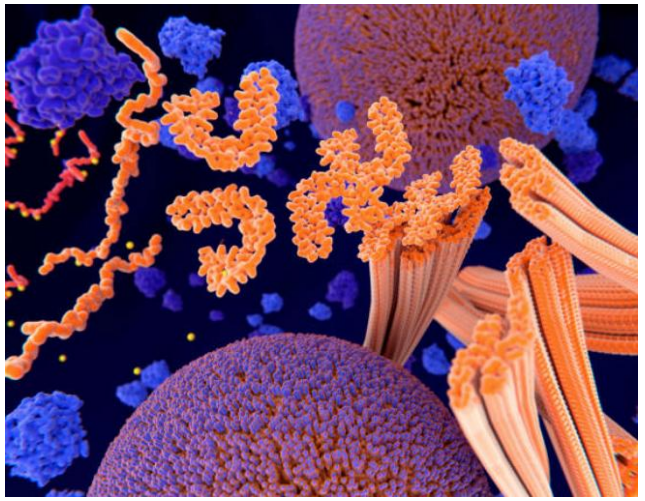


Drs. Kristen Whitney, John Crary, Mt Sinai Medical School, NY

How can we cure tauopathy?
Lets target tau itself to prevent aggregation and remove toxic tau molecules



Tau protein aggregates into ‘tangles’



Antibodies to tau that work OUTSIDE cells recent failure in clinical trial

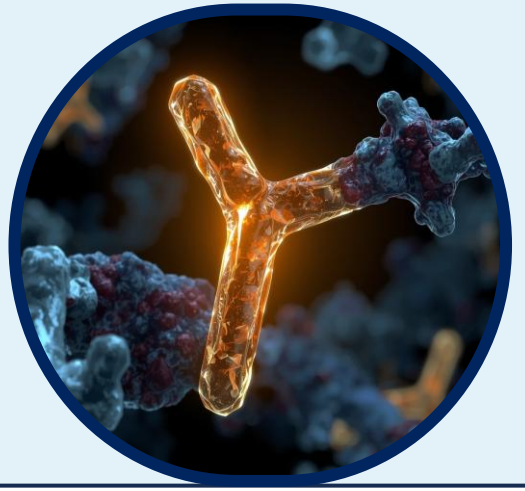
FIERCE Biotech | Biotech | Research | Medtech | CRO | Special Reports | Trending | Fierce 50

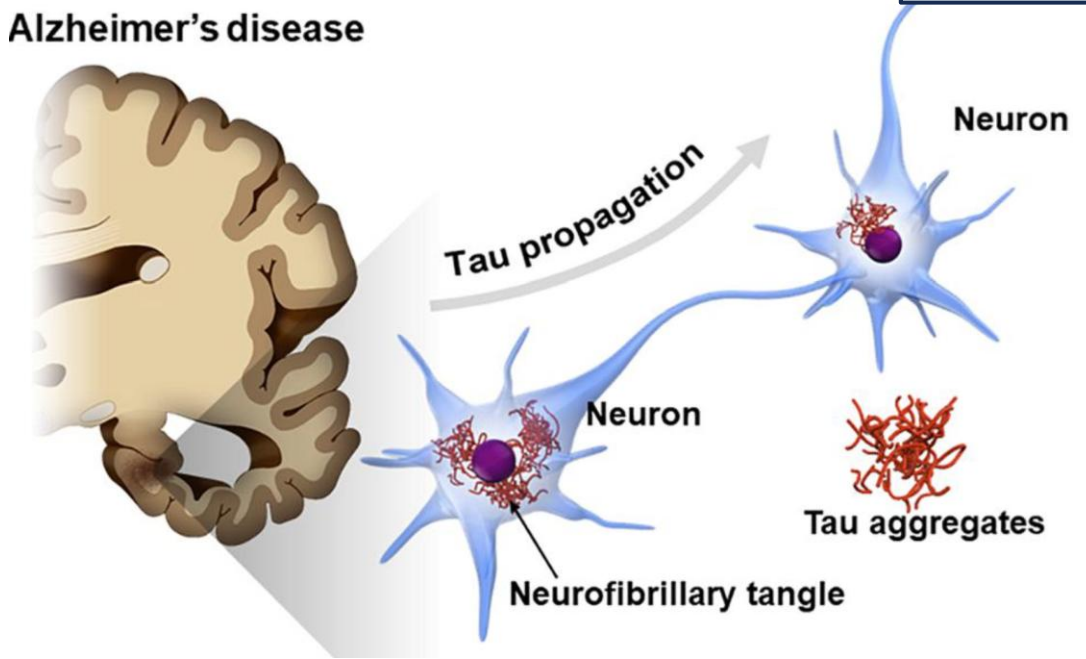
BIOTECH

J&J's $5B Alzheimer's hope fades as anti-tau antibody posdinemab flops in phase 2

By Nick Paul Taylor · Nov 24, 2025 9:40am

Our approach: Intrabodies work INSIDE cells to reduce tau



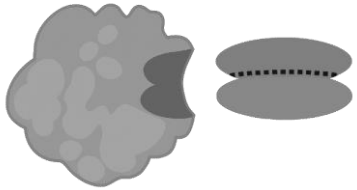


c.10,000 times as much toxic tau inside cells compared to outside cells

Tau Intrabodies have a Bi-Functional Mechanism of Action

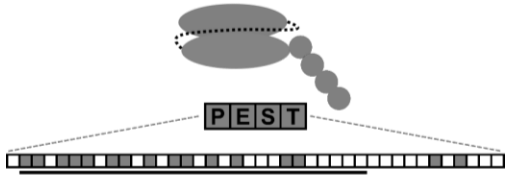
Bind Target: Tau

Intrabody domain binds to pathogenic target inside the cell.



Degrade Tau

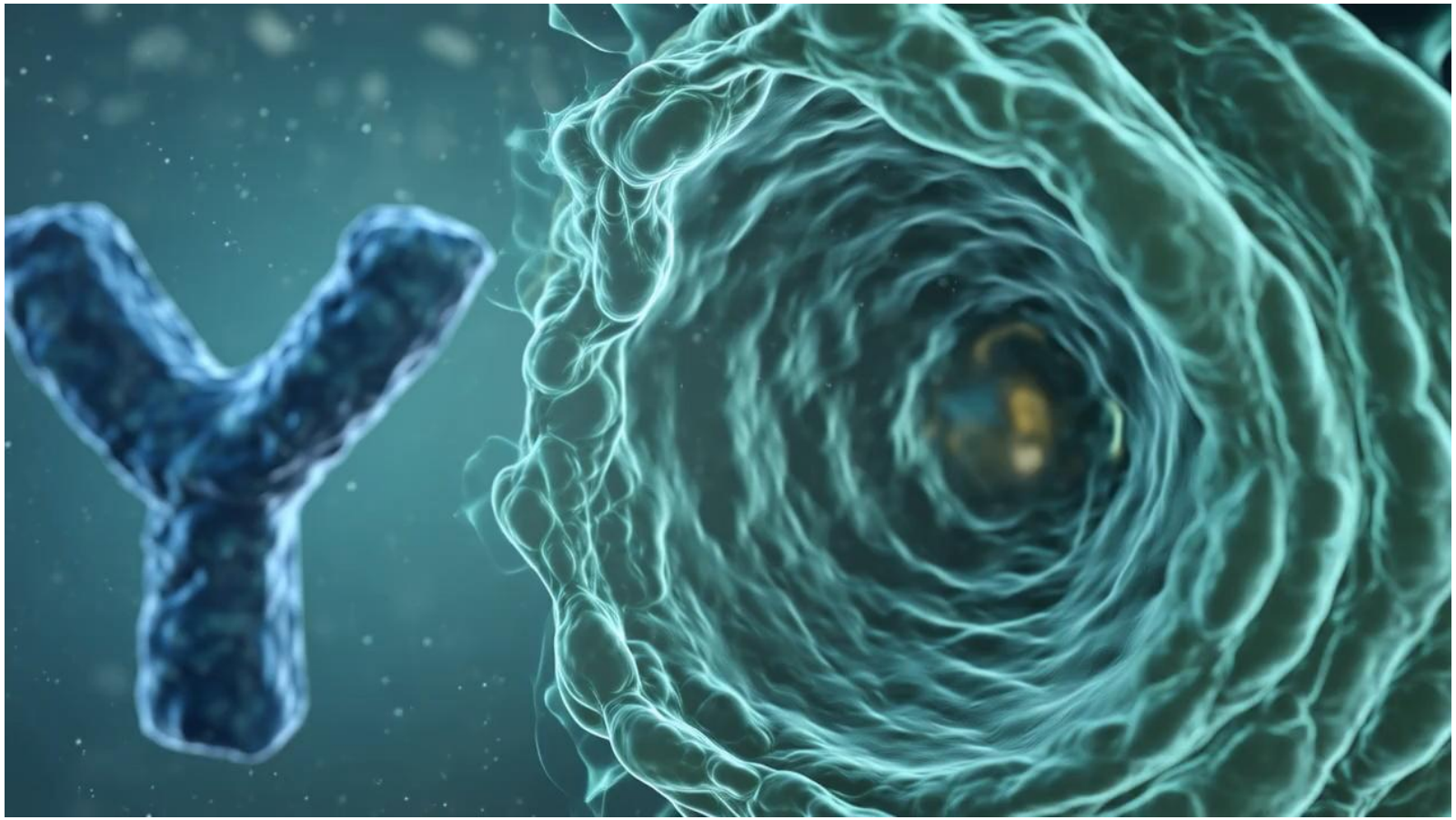
Modular PTAP degron enables programmable proteasomal degradation



Improve Cell Health

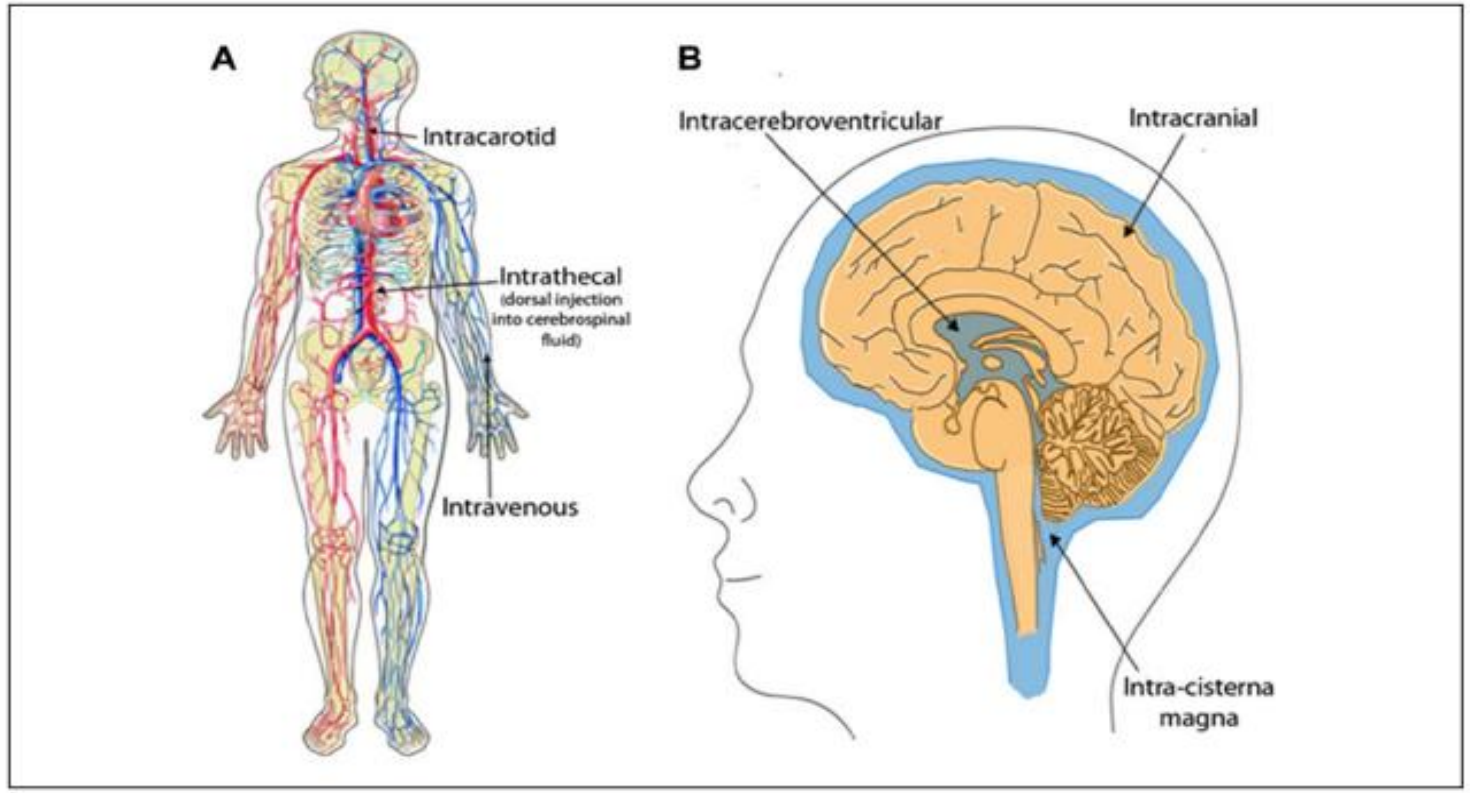
Controllable clearance of any intracellular target protein.

Intrabody binds and degrades toxic tau protein inside cells

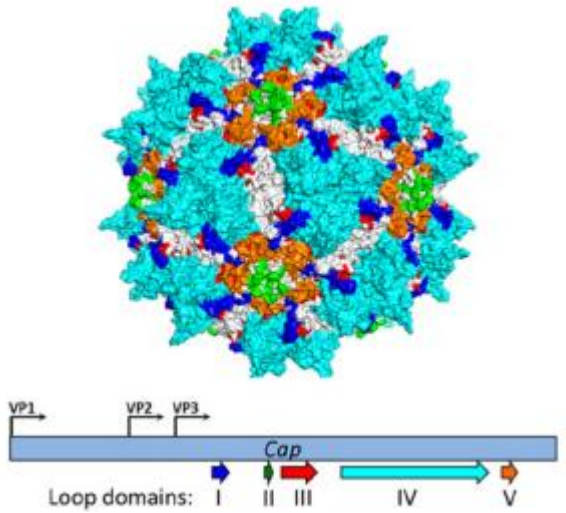


Dr. David Butler

Deliver tau-degrading intrabody as a gene therapy: ‘one and done’ treatment



AAV



https://schafferlab.berkeley.edu/wp-content/uploads/2022/12/3.pdf

Summary of current approaches to lower toxic tau in the brain

Approach	Administration	Clinical results to date
Antisense oligonucleotides (ASOs) e.g. Ionis, Biogen, Roche	Injected into the spinal cord CSF by lumbar puncture every 8-12 weeks	Promise in patients; some negative responses to repeated intrathecal injections
Antibodies to extracellular tau e.g. posdinemab	Vascular infusions every 4 weeks	Failed in Phase 2
Intrabodies to intracellular tau (our approach)	'One and done' gene delivery	In preclinical stages, benefit in organoids, now testing in vivo in animals Progressing toward a clinical trial

Thank you all!

- For raising awareness, with friends, family, healthcare and government representatives
- For supporting research efforts to combat FTD and related diseases
- For participating in studies
- For sharing experiences and helping others cope with neurodegenerative diseases

Happy to take Questions!

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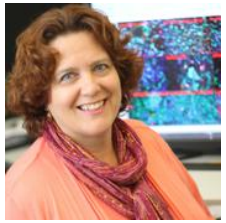
Acknowledgements: It takes a village!

NSCI
NEURAL STEM CELL INSTITUTE

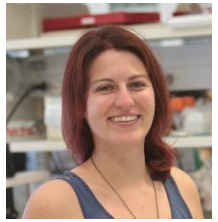

Susan Goderie


David Butler


Akinsola Akinyemi


Taylor Bertucci


Natasha Rugenstein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