Treating Parkinson's Disease in human iPSCs-derived neurons and mice models

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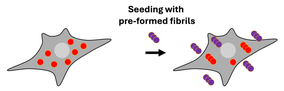
What do we do in the lab ?

From tool development to disease modeling in vitro as well as in vivo, in Poul Henning Jensen's group we are studying the protein responsible for Parkinson's Disease (PD) and investigating potential ways to treat this devastating brain pathology. Alpha-synuclein, a 40 amino acid long protein is normally present in neuronal terminals, facilitating synaptic transmission. In pathological conditions, it can be over-expressed, phosphorylated and can aggregate, causing various cellular dysfunctions and ultimately neuronal death. The molecular mechanisms behind this toxicity remain unsolved and no cure for PD is yet approved or available.

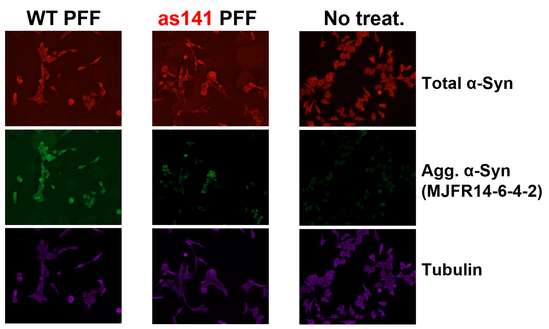
A "magic" tool : Pre-formed fibrils invisible to the aggregate-specific antibodies

Pre-Formed Fibrils (PFFs) are small alpha-synuclein aggregates formed in vitro that trigger aggregation in cells and animals.

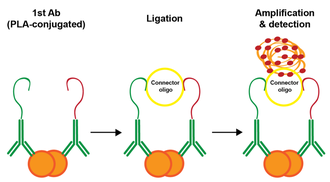


Fibrils generated from α-syn including an added glycine on its C-terminal (S129A,141G hu-aSyn) are not recognizable by the aggregate-specific antibody MJFR-14-6-4-2 and enable detection of only endogenous aggregates in cells.

OLN-AS7 cells were treated for 24h with either WT PFF or Stealth PFF at a concentration of 14 µg/ml before analyzing by immunocytochemistry for tubulin (purple), aggregates α-syn (MJFR-14-6-4-2) (green) and total α-syn (LB509) (red) [1]



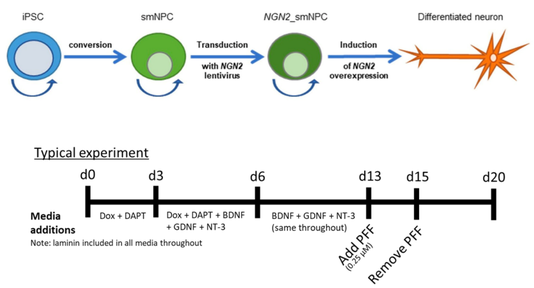
Proximity Ligation Assay (PLA) to detect early α-syn aggregates



Two different antibodies recognize two different epitopes. When the two antibodies are in close proximity, their complementary proximity probes ligate to a connecting oligonucleotide and a signal is amplified so that a single pair of antibodies can be visualized by fluorescent microscopy, generating a single dot on the image (see Figure below) [2].

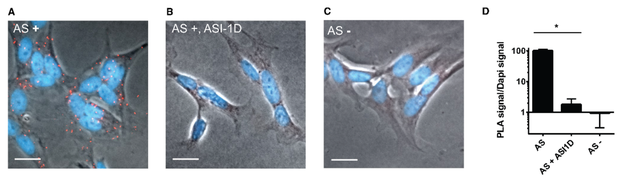
Modeling PD in vitro : The iNeuron model

iPSCs-derived neurons from healthy donors or PD patients can be used to model the disease in vitro.

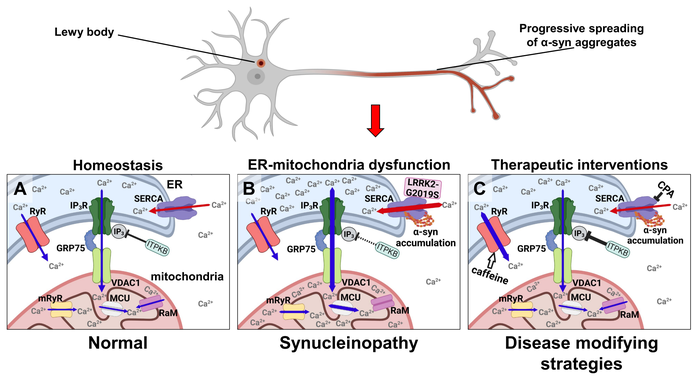


A new way to treat Parkinson's Disease

Aggregated alpha-synuclein disrupts calcium homeostasis by binding to and over-activating the ER-bound calcium pump SERCA [3].



SERCA/Synuclein PLA signal in SH-SY5Y cells is present only when alpha-synuclein expression is induced and when ASI-1D, a compound known to inhibit alpha-synuclein aggregation, is absent. [3]



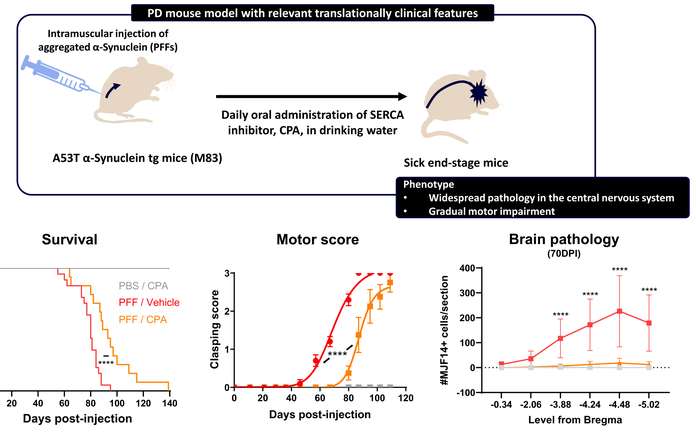
Alpha-synuclein aggregates bind to and over-activate SERCA resulting in a clacium dyshomeostasis that leads to oxidative stress, increase in reactive oxygen species (ROS), mitochondrial dysfunctions and, ultimately, cell death. The proposed therapeutic strategy is to rescue this phenotype by targeting different players of the calcium homeostasis regulation [4].

Come and give us a visit !

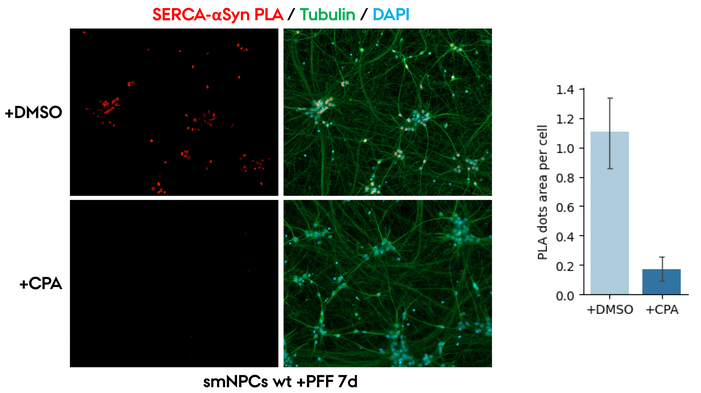
The lab is constantly looking for motivated students, take a look at

`dandrite.au.dk/people/research-groups/jensen-group`

Testing the drug in vivo



Testing the drug in vitro



Proximity-ligation assay between SERCA and alpha-synuclein in smNPCs neurons seeded with PFF and treated with or without the SERCA inhibitor CPA.

References

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