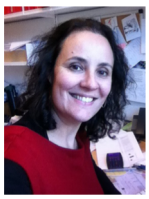
AARHUS UNIVERSITY
DEPARTMENT OF BIOMEDICINE

Neuronal and immune changes in models of Parkinson's Disease



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Team: 1 lektor, 1 TAP, 3 Ph.d. students, 1 postdoc

Background

Parkinson's Disease

Parkinson's disease (PD) is characterized by the **progressive neurodegeneration** in substantia nigra (SN), and the presence of aggregated **α-synuclein** (α-syn) throughout the CNS. α-Syn plays a central role in PD and mutations or the accumulation of the normal α-syn can lead to PD. In addition to the neuronal changes in PD brain numerous evidence show the activation and proliferation of the macrophage cells in brain: the microglia. Microglia is essential for neuronal maintenance and survival, and it senses any change occurring in neighboring neurons

The '**Braak hypothesis**' of α-syn CNS pathology states that abnormally aggregated α-syn is transmitted among neurons. Normally modified α-syn released from **neurons** will be efficiently cleared by **microglia**, but upon failure of this event other neurons could uptake the α-syn. In turn, this prion-like α-syn will further promote mishandling of intracellular α-syn that can ultimately lead to neuronal dysfunction.

We propose that **neuroinflammation** plays important role in PD and could contribute to the **neuronal survival and the prion-like spreading** of misfolded α-syn. This neuroinflammation seems to involve not only microglia, but also peripheral immune cells such as monocytes.

Mishandling of α-syn in neurons leads to cellular changes that if unresolved, results ultimately into cell death. Therefore we further study **neuronal changes** induced by α-syn as well as the **pathology** of α-syn associated to these changes.

Projects and techniques

Research focus

1) To study early neuronal changes induced by α-syn in brain 2) to characterize the response of inflammatory cells to those changes both locally and peripherally 3) to understand the role of the immune cells in the prion-like spreading of α-syn 3) to develop and test novel neuroprotective strategies focusing on the neuroinflammatory event in PD.

Parkinson's Disease models

A rat PD model based in local intracerebral injections of **viral vector** coding for h-α-syn (human-α-synuclein). This leads to unilateral overexpression of h-α-syn in adult rat brain with a subsequent progressive neurodegeneration of neurons in SN. This allows us to use the contralateral uninjected side (left) as an internal control [Fig. 3.].

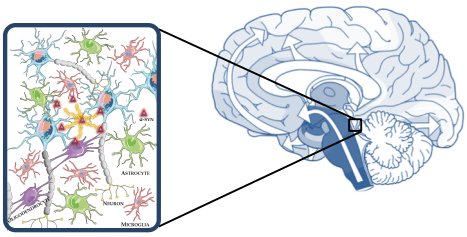
Several **transgenic** lines overexpressing the h-α-syn are also used in the lab. These animals exhibit progressive signs of neurodegeneration and motor defects, and are very useful to study early vs. late changes induced by α-syn overexpression.

Alternative models of PD are also generated using **intracerebral injections of aggregated** α-syn that recapitulates the prion like spreading of the protein in PD.

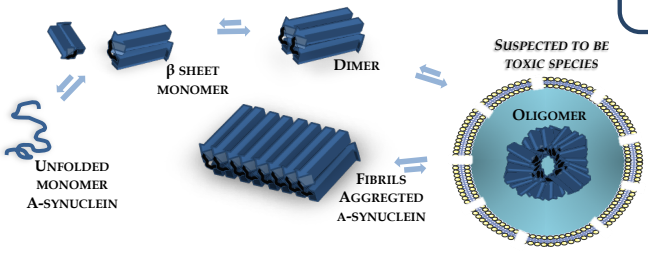
Lab environment

You will be working in **an active international lab**, where we will teach about neurodegeneration, using in vivo and also neuroanatomical techniques. Our projects are funded by the M.J Fox Foundation, Danish Parkinson Foundation and Lundbeck Foundation, among others. We seek for **engaged students with team spirit** and the desire to learn and enjoy the research environment.

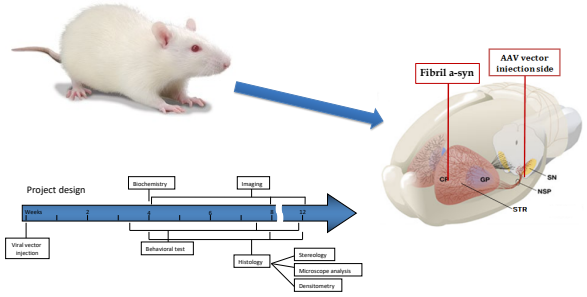
Brain: more than neurons



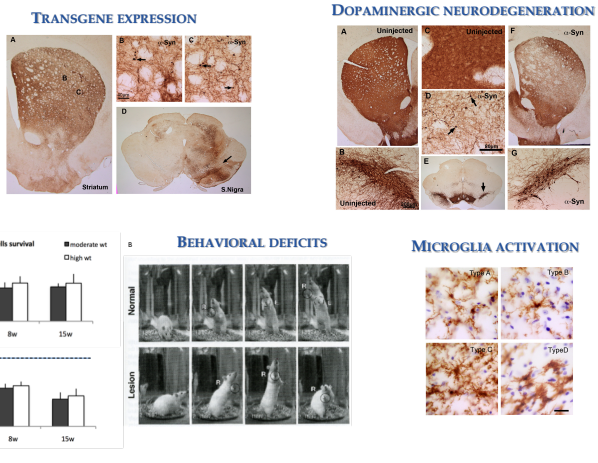
Pathological Aggregation of α-synuclein



In vivo PD modeling



Behavioral and post-mortem analysis



EXAMPLE OF RECENT PUBLICATIONS

1. Phan JA, Stokholm K, Jakobsen S, Vang K, Gjedde A, Landau AM, **Romero-Ramos M**. Early synaptic dysfunction induced by α-synuclein in a rat model of Parkinson's disease. **Sci Rep**. 2017 Jul 25;7(1):6363
2. Jimenez-Ferrer I, Jewett M, Tontanahal A, **Romero-Ramos** M, Swanberg M. Allelic difference in Mhc2ta confers altered microglial activation and susceptibility to α-synuclein-induced dopaminergic neurodegeneration. **Neurobiol Dis**. 2017 Jul 20.
3. Tentillier N, Etzerodt A, Olesen MN, Filiz Rizalar S, Jacobsen J, Bender D, Moestrup SK and **Romero-Ramos M**, Anti-inflammatory modulation of microglia via CD163-targeted glucocorticoids protects dopaminergic neurons in the 6-OHDA Parkinson's disease model, **J. Neurosci.** 2016, 36: 9375-90.