Models of Parkinson´s disease in mice

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MODEL DESCRIPTION

Parkinson's disease (PD) is a progressive long-term neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta projecting to the striatum along the nigro-striatal pathway. The striatal dopamine depletion causes the typical motor symptoms of PD like bradykinesia, tremor, rigidity and postural abnormalities. Another key pathological feature of PD is the presence of intracellular protein inclusions containing alpha-synuclein in many neuronal cells within regions affected by the neurodegenerative process. Alpha-synuclein protein aggregates become toxic when clustered together forming insoluble complex structures called Lewy bodies.

Redoxis provides different and complementary mouse models of PD, one of which is the unilateral intrastriatal lesion with the 6-Hydroxydopamine (6-OHDA) toxin to mimic disease hallmark. The use of toxin-mediated models like the 6-OHDA has been widely used in rodent models of Parkinson's disease as it can reliably reproduce the selective dopaminergic loss. Other models, like transgenic PD models or AAV vector mediated models can be set up on demand to accommodate research requirements.

6-OHDA LESION AND TREATMENT

Mice with the 6-OHDA lesions are widely used as reliable model for understanding of the mechanisms underlying parkinsonian symptoms, since it recapitulates the changes in basal ganglia circuitry and pharmacology observed in parkinsonian patients. Moreover, the 6-OHDA lesion-model is a great tool to study the effects of symptomatic, neurorestorative, or neuroprotective treatments for Parkinson's disease.*

VIRAL VECTORS

An additional opportunity for modelling Parkinson´s Disease consists in the delivery of mutated genes to specific neuronal populations using viral vectors. Using viruses specialised mechanisms to transport their genomes inside the cells, coding regions of the gene of interest can be inserted into the target cells. This process can be performed inside a living organism and can be used, for example, to induce a disease model (e.g. alpha-synuclein overexpression model) or to provide treatments as the target cells will start using the new transduced gene to perform its function.*

BEHAVIORAL TESTS AND IMMUNOHISTOCHEMISTRY

A battery of behavioural test like cylinder test and open field test can be provided to monitor disease modifying effects and drug-induced behaviours.
Our histology laboratory is equipped for all types of tissue analysis and can accommodate a variety of analyses and methodologies to facilitate a broad spectrum of studies. We have developed histological assays, IHC protocols and unique scoring methods for numerous project types with standard and customised read outs. Finally, we are always willing to discuss set up on demand assignments based on customer specific needs.

*Other options are available including standard strains and genetically modified strains

Read more:
Impact of the lesion procedure on the profiles of motor impairment and molecular responsiveness to L-DOPA in the 6-hydroxydopamine mouse model of Parkinson´s disease. Francardo et al. *Neurobiol. Dis.(2011)*

6-OHDA lesion

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Unilateral injection of 6-OHDA in mice striatum produces a partial lesion of the nigro-striatal dopaminergic pathway along with significant motor disturbances similar to those of PD patients. This model is commonly used to test neuroprotective and neurorestorative drug candidates.

A more severe model can be achieved injecting the 6-OHDA in the medial forebrain bundle (MFB) region, producing a complete loss of both striatal dopaminergic fibers and nigral cell bodies followed by a severe motor deficit.

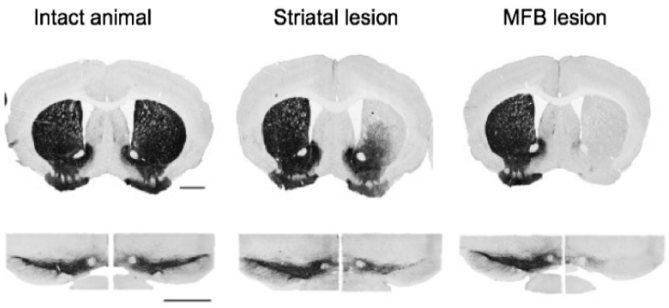

Figure 1. Striatum and substantia nigra representation from intact or 6-OHDA lesioned mice. The 6-OHDA toxin can be injected in the striatum or MFB area to induce partial or complete depletion of the dopaminergic neurons and fibers. (Courtesy of Francardo. V).

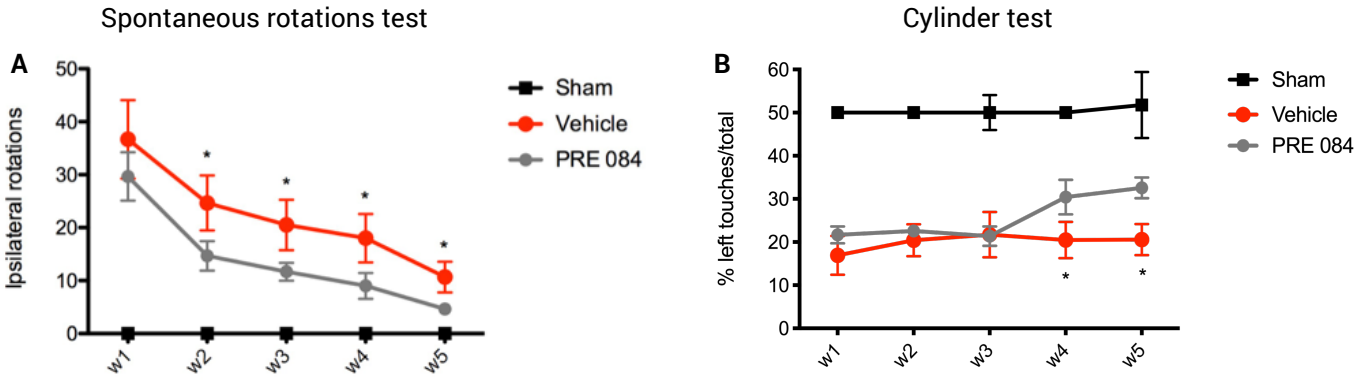

Figure 2. Chronic treatment of 6-OHDA-lesioned mice with the neuroprotective drug PRE-084 induces motor recovery.
The 2 different behavioral tests were assessed once a week in mice treated with either PRE-084 (0.3mg/kg) or saline solution. Sham animals are naïve, non-treated animals. Results are expressed as number of spontaneous ipsilateral rotations during a 10 min test session (A), or as a percentage of supporting wall *contacts (B) performed with the paw contralateral to the lesion (left paw). RM ANOVA, p<0.05 versus PRE 084 treated animals.*

INDUCTION AND EVALUATION

Disease induction protocol:	6-OHDA toxin injection day 0
Strain:	C57BL/6 (or Tg mice)
Suggested group size:	8-10 mice/group
Duration:	7 or 35 days
Onset:	immediate (d0)
Positive controls:	PRE-084 (neuroprotective drug)
Clinical signs:	Behavioural tests and visual behavior observations
General health:	Weight
Histology	e.g. TH+ cells and fibres in Striatum and SNpc.

6-OHDA MODEL OUTPUT:

- Drug testing,
- Drug candidate evaluation,
- Compound administration and bioavailability,
- Behavioral studies,
- Immunohistochemistry and microscopy,
- Flow cytometry for microglia.

Read more:

Dramatic differences in susceptibility to L-DOPA-induced dyskinesia between mice that are aged before or after a nigrostriatal dopamine lesion. Bez et al. *Neurobiology of Disease* (2016)
Pharmacological stimulation of sigma-1 receptors has neurorestorative effects in experimental parkinsonism. *Brain J. Neurol.* (1998-2014)