Annex B

Parkinson's disease

ANIMAL MODELS CURRENTLY AVAILABLE

Genetic models

TARGETED GENE	DESCRIPTION[1]	PHENOTYPE (Y/N; BRIEF DESCRIPTION)	NEURONAL DEGENERATION (Y/N; BRIEF DESCRIPTION)	PROTEINOPATHY/ AGGREGATES (Y/N; BRIEF DESCRIPTION)
Transgenic				
Alpha synuclein	Mice or rats overexpressing full length or part of alpha synuclein mutated (A30P, A53T, A30P/A53T) or wild type	Little behavioral effect. In some models alteration of gastrointestinal function.	In most of the models no neuronal loss but alteration in dopamine transmission.	Alpha synuclein deposits widespread in the brain
LRRK2	Mice overexpressing mutant (R1441G or G2019) or WT LRRK2	Little or no motor defects	no	Modest increase in total and phosphorylated tau
Models for the other genes mutated in PD (parkin, Pink1, DJ1)	KO transgenic mice	Little behavioral effect (mostly moderate decline in locomotor activity)	In most of the models no neuronal loss but alteration in dopamine transmission; mitochondrial defects (parkin, Pink1 mutants); increased susceptibility to pro-oxidant toxins (DJ1-mutants)	no
Aphakia (ak)	Mice deficient in Pitx3	Dysfunction due to dopaminergic degeneration	Loss of dopaminergic neurons in the substantia nigra but less in VTA	no
MitoPark mouse	Mitochondrial transcription factor A (Tfam) KO in midbrain DA neurons, causing reduced mtDNA	Delayed, progressive reduction of locomotor activity, ameliorated by L-DOPA	Adult-onset nigrostriatal degeneration with reduction of dopamine levels.	Intracellular inclusions positive for mitochondrial protein markers (no synuclein)

	expression and respiratory chain defects			
Engrailed mouse	Ablation of homeobox transcription factors Engrailed-1 and Engrailed-2 (required for survival of SNc dopaminergic neurons): *En1+/-;En2-/-*	Subtle motor deficits	Loss of SNc neurons and striatal dopamine	no
c-Rel mouse	Mice carrying null mutation in DNA binding protein c-Rel (part of the NFkB complex): *c-Rel−/−*	Age-dependent locomotor and gait-related deficits responsive to L-Dopa	Age-dependent loss of SNc dopaminergic neurons and striatal terminals; reduction of striatal dopamine and homovanillic acid levels	Increased alpha-synuclein immunoreactivity in the SNc
Nurr1 mouse	Heterozygous KO of transcription factor Nurr1 (required for development and maintenance of dopamine neurons): *Nurr1 +/−*	Decreased rotarod performance and locomotor activities	Age-dependent nigral cell loss and reduction in striatal dopamine and dopamine-mediated signaling. Increased vulnerability to MPTP	no
Atg-7 mouse	Conditional deletion of autophagy-related (Atg) gene 7 in SNc neurons	No PD-like phenotype	Age-related loss of dopaminergic neurons and striatal dopamine	Accumulation of low-molecular-weight alpha-synuclein and ubiquitinated protein aggregates
Virus-induced				
Alpha synuclein	Cav-viruses over expressing human alpha synuclein in mice or rats	Unilateral injection of the virus in the striatum. Loss of dopaminergic neurons. The advantage of the Cav is that as compared to other viruses it is less immunogenic. Rotation	Loss of dopaminergic neurons	Alpha synuclein inclusions

		behavior can be analyzed		
Alpha synuclein	AAV expressing full length alpha synuclein in rat or monkeys	Unilateral injection of the virus in the striatum or the cerebral cortex. Loss of dopaminergic neurons. When injected in the cerebral cortex it can be combined with a 6-OHDA lesion of nigral dopaminergic neurons	Loss of dopaminergic neurons of alteration of cortical neurons depending on the site of injection. It can mimic end stage Parkinson's disease in which Alpha synuclein inclusions are found in the cerebral cortex.	Yes when injected in the striatum. It can also mimic end stage Parkinson's disease in which Alpha synuclein inclusions are found in the cerebral cortex.
LRRK2	Cav-viruses or AAV over expressing human wild type or mutated LRRK2 in mice or rats	Unilateral injection of the virus in the striatum. Loss of dopaminergic neurons. The advantage of the cav is that as compared to other viruses it is less immunogenic. Rotation behavior can be analyzed	Loss of dopaminergic neurons	N
Non-mammalian models				
Drosophila	Overexpression of wt or mutant human alpha-synuclein	Progressive loss of climbing activity	Age-dependent and selective loss of dopaminergic neurons	Fibrillary inclusions containing alpha-synuclein
	Parkin or PINK1 KO or overexpression of mutated forms	Loss of climbing activity	Mitochondrial defects and moderate dopaminergic degeneration	no
	DJ1-beta (homolog of human DJ1) KO	?	Enhanced susceptibility to pro-oxidant toxins	no
	LRRK2 KO or overexpression of mutated forms	no	no	no
Zebrafish	Parkin or PINK1 KO	Moderate reduction in locomotor activity	Moderate loss of dopaminergic neurons, reduced mitochondrial complex I activity and increased susceptibility to toxins	no

	DJ1 KO	no	Increased susceptibility of dopaminergic neurons to toxins	no
	Deletion of functional domain WD40 of LRRK2	Locomotor defects	Loss of dopaminergic neurons	no

[1]*Expression of mutant gene, overexpression of WT gene, knock-out, etc.*

Non-genetic (toxic/pharmacological) models

TOXIN	SYSTEMIC/LOCAL ADMINISTRATION[2]	PHENOTYPE (Y/N; BRIEF DESCRIPTION)	NEURONAL DEGENERATION (Y/N; BRIEF DESCRIPTION)	PROTEINOPATHY / AGGREGATES (Y/N; BRIEF DESCRIPTION)
6-OHDA	Local Nigral, MFB or striatalstereotaxic injection	Apomorphine/amphetamine-induced rotations; the striatal injection produces a progressive partial degeneration over about 4 weeks, while nigral/MFB injection causes complete, fast evolving lesions (within 1 week). Good for analysis of LID.	Yes, there is loss of DA neurons, but not of other neurons. The striatal injection produces immediate terminal damage, followed by delayed loss of nigral cell bodies; nigral microglial activation precedes actual loss of DAergicneurons	no
MPTP	Systemic i.p. or s.c.via osmotic pump in mice, i.p., i.m. or intra jugular in monkey. Recently it has been administered intra-nasaly	Little phenotype in mice and rather a hyperactivity, akinesia and rigidly in monkey, resting tremor in green monkeys and transient rest tremor in macaques. Can be combined with lesions of other neurotransmitter systems such as cholinergic neurons in the PPN to produce gait and balance disorders or norepinephrine neurons in the locus coeruleus to produce intellectual impairment. Good for analysis of LID.	Yes, loss of dopaminergic neurons reproducing the selective vulnerability seen in human. Neuroinflammatory processes in monkey but not in rodents.	no
Rotenone	Systemic i.v., s.c. or i.p. via osmotic	Severe phenotype including akinesia, GI dysfunction, gait and	Loss of dopaminergic and non dopaminergic	Alpha synuclein and

	pump (rats) Intra-gastric or oral administration (mice) for investigation of PD-related GI dysfunctions	balance disorders but not specific for dopaminergic neurons Less severe phenotype; impaired performances at the rotarod test; GI dysfunction (reduced fecal output following oral adm.)	neurons (widespread lesions). Glial cells also affected Moderate SNc lesion (oral>intragastric);	tau pathology Trans-synaptic transmission of synuclein pathology along the brain-gut axis (intragastric adm.)
Paraquat	<u>Systemic</u> <u>i.p. (mice)</u>	No clear motor deficits	Moderate SNc cell loss; decreased striatal TH immunoreactivity	Up-regulation and aggregation of synuclein in the SNc
Annonacin	<u>Systemic</u> i.v., via osmotic pump	Severe phenotype including akinesia, gait and balance disorders but not specific for dopaminergic neurons. Reproduces an atypical form of PD in the French Caribbean	Loss of dopaminergic and nondopaminergic neurons reproducing the pathology seen in an atypical form of PD in the French Caribbean	Tau pathology
l-trans-pyrrolidine-2,4-dicarboxylate(EAATsinhibitor)	<u>Local</u> Intra nigral	Rotation after unilateral lesion	Selective loss of DA neurons	Alpha synuclein pathology
LPS alone or associated to 6-OHDA	<u>Local or systemic</u> Intra nigral or i.p.	???	Loss of dopamine neurons neuroinflammatory processes	no

[2]*Brief description of the procedure*

CELLULAR MODELS CURRENTLY AVAILABLE

CELL TYPE	DESCRIPTION	NEURONAL DEGENERATION (Y/N; BRIEF DESCRIPTION)	PROTEINOPATHY/ AGGREGATES (Y/N; BRIEF DESCRIPTION)
SH-SY5Y	Human neuroblastoma cells	Sensitivity to PD-related toxins; mitochondrial defects, proteotoxicity and cell death triggered by transfection with PD-associated mutant genes	Synuclein aggregation can be triggered under specific conditions
PC12	Rat pheochromocytoma	Sensitivity to PD-related toxins	Synuclein aggregation can be triggered under specific conditions
MES	Hybrid rat mesencephalic-neuroblastoma cells	Sensitivity to PD-related toxins	Synuclein aggregation can be triggered under specific conditions
Primary neuronal cultures	Cultured dopaminergic neurons from embryonic mesencephalon	Sensitivity to PD-related toxins; synuclein overexpression-induced cell death	Synuclein aggregation can be triggered; cell-to-cell synuclein propagation can be observed
Cybrids	Hybrid cell lines obtained by fusing cells that lack mtDNA with platelet mtDNA from PD patients	Defects of the mitochondrial ETC	no
iPS	Induced pluripotent stem cells re-programmed from human fibroblasts	PD-related biochemical defects from donor cells are substantially maintained (*"brain in a dish"*)	Synuclein aggregation can be triggered