

Parkinson's disease mouse models in translational research

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Abstract Animal models with high predictive power are a prerequisite for translational research. The closer the similarity of a model to Parkinson's disease (PD), the higher is the predictive value for clinical trials. An ideal PD model should present behavioral signs and pathology that resemble the human disease. The increasing understanding of PD stratification and etiology, however, complicates the choice of adequate animal models for preclinical studies. An ultimate mouse model, relevant to address all PD-related questions, is yet to be developed. However, many of the existing models are useful in answering specific questions. An appropriate model should be chosen after considering both the context of the research and the model properties. This review addresses the validity, strengths, and limitations of current PD mouse models for translational research.

Introduction

Age-related neurodegenerative diseases are an increasing burden to an aging population. Parkinson's disease (PD), the most common neurodegenerative movement disorder, frequently occurs in an idiopathic form without clearly defined cause. Familial forms of PD, arising from monogenic mutations, account for a minority of PD cases. The

clinical course of both idiopathic and familial forms of PD is believed to be influenced by environmental and genetic risk factors. Mouse models are powerful tools in PD translational research. However, an appropriate model should be chosen after considering both the model characteristics and the research context.

The Parkinson's disease puzzle

PD is a progressive neurodegenerative disorder clinically characterized by the cardinal symptoms of resting tremor, bradykinesia, cogwheel rigidity, and postural instability (Jankovic 2008). Responsiveness to L-3,4-dihydroxyphenylalanine (L-DOPA) and brain imaging distinguish PD from other disorders (D'Costa et al. 1995; Isaias and Antonini 2010). The pathological hallmarks of PD are loss of dopaminergic cells in the substantia nigra pars compacta and subsequent loss of dopamine innervation in the striatum (Forno 1996). Motor symptoms are the most obvious consequence of this nigrostriatal neurodegeneration. However, not only the basal ganglia but also other parts of the central nervous system as well as the autonomic nervous system are affected. A wide range of resulting non-motor symptoms can affect the patient's quality of life (Langston 2006; Lees 2009). It has been assumed that at least some subforms of PD start not with motor but non-motor symptoms such as hyposmia, rapid eye movement sleep behavior disorder (RBD), constipation, depression, reduced cardiac [123 I]metaiodobenzylguanidine (MIBG) uptake, and, possibly, reduced color discrimination (Chaudhuri et al. 2006; Fujishiro et al. 2008; Hawkes 2008; Katzenschlager and Lees 2004). There is also a broad consensus that neurodegenerative processes in PD start many years before the actual onset of clinical

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manifestations (Savica et al. 2010; Tolosa et al. 2009). The not yet fully understood sequential plan underlying PD pathogenesis seems to correlate with clinical and pathological features (Hawkes et al. 2010). Lewy bodies, the histological hallmarks of PD, are α -synuclein-positive intracellular inclusions that are already present during the prodromal phase (Fearnley and Lees 1991). A yet asymptomatic, incidental Lewy body disease has been proposed (Markesbery et al. 2009). However, it is not yet fully understood if Lewy bodies have more protective or more destructive effects. Motor symptoms start only in the late phase of nigrostriatal degeneration, when 50–80% of nigral dopaminergic neurons are already lost (Bezard et al. 2001; Braak et al. 2003; Greffard et al. 2006). At this stage, nonmotor features remain frequent and clinically significant because they largely contribute to impaired quality of life and shortened life expectancy. Neuroprotective treatments are not yet available but are one of the priorities in current PD research. However, reliable biomarkers for early diagnosis and disease state identification are not yet available (Gasser 2009a; Schapira et al. 2009).

Consequently, at present, the diagnosis of PD is based on the above-mentioned characteristic clinical motor features. Importantly, the currently recognized monogenic familial forms of PD do not demonstrate the same clinical features as those of sporadic late-onset forms of PD. Genetic forms can present more pronounced psychiatric features and lack nonmotor symptoms. Nevertheless, the phenotypical overlapping between familial and idiopathic PD is sufficient to dissect the commonly involved pathways. These include mitochondrial dysfunction, oxidative stress, protein misfolding, protein degradation, protein aggregation, and inflammation (Schapira and Tolosa 2010). Evidently, a better understanding of the molecular basis of PD will open new routes to diagnosis and therapy (Pienaar et al. 2008; Robinson 2010). On the other hand, it will influence the choice of adequate models for translational research.

Animal models for translational research in PD

Progress in understanding the etiology of PD has provided candidate targets for neuroprotective and neurorescue interventions. However, until now, no potential protective treatment has received regulatory approval (Rascol 2009). One reason for this is the lack of good PD animal models for preclinical translational research. Animal models should fulfill specific requirements for the testing of neuroprotective therapies for PD. First, the model should induce reproducible nigral lesions. Second, the loss of dopaminergic neurons should be stable, without spontaneous recovery. Third, the model should provide a time window for the application of potential neuroprotective

therapies (Emborg 2004). Ideally, a successful neuroprotective agent should prevent further behavioral changes, progressive biochemical deficits, and neurodegeneration. Thus, neuroprotection requires intervention when there are still cells left to be protected. Later interventions should be regarded as restorative strategies.

Current status and remaining challenges

Arvid Carlsson's research led to the development of L-DOPA-based treatments (Andersen 2009). Today, L-DOPA remains the gold standard treatment for PD. However, the drug has a wide range of adverse effects, most notably motor fluctuations and dyskinesias. Pharmacological strategies that avoid pulsatile dopaminergic stimulation have a substantial ameliorative effect on these syndromes. Despite these advances, disease progression remains unaffected (Lang and Obeso 2004). Finally, deep brain stimulation is the most recent symptomatic treatment that continuously and substantially reduces parkinsonian motor symptoms, whereas gait deterioration and nonmotor features continue to progress (Hamani et al. 2010).

Despite these therapeutic advances, PD patients continue to suffer from a severe reduction in quality of life. The development of interventions to stop or slow disease progression is therefore a major goal (Schapira and Tolosa 2010). The progress of this endeavor requires a better understanding of disease etiology and subtype stratification (Rajput et al. 2009). Importantly, early diagnosis enables the initiation of neuroprotective or other therapeutic interventions at less advanced stages of the disease.

Current mouse models for PD

PD mouse models are expected to closely match human pathology. The most important signs to replicate are motor symptoms, Lewy body formation, neuronal cell loss in the basal ganglia, age-related disease progression, and non-motor symptoms. None of the current models satisfies all of these criteria. However, many models fulfill a subset. Empirical choices of adequate models to answer specific questions in translational research need to consider, case by case, the model-specific advantages and limitations.

Pharmacological and neurotoxic PD models

Reserpine

One of the earliest developed PD models was the pharmacological reserpine model, which prevents the storage of

dopamine in presynaptic terminals, resulting in dopamine depletion in the striatum (Carlsson et al. 1957; Steg 1964). Reserpine rabbit models helped to elucidate the critical role of dopamine in the pathogenesis of PD. This finding led to the discovery of dopaminergic drugs such as L-DOPA. Despite this groundbreaking success, the reserpine model has significant limitations. Reserpine does not exclusively deplete dopamine and norepinephrine but all monoamines in a transient fashion. Another limitation of this model is that transient depletion does not mirror the progressive dopamine depletion in PD. In addition, the reserpine model does not reflect the histopathology of PD.

6-Hydroxydopamine (6-OHDA)

A few years after publication of the reserpine model, in the 1960s, nigrostriatal pathology was recognized as a primary factor for PD. In this context, the first neurotoxic models, aiming to reproduce nigrostriatal pathology, were established (Table 1). One neurotoxin found to induce PD was the dopamine analog 6-OHDA (Ungerstedt et al. 1974). 6-OHDA can be taken up into dopaminergic terminals via dopamine transporters. Inside the cell, it is metabolized, resulting in the production of hydrogen peroxide and free radicals, which induce neuronal death via mitochondrial dysfunction. 6-OHDA cannot cross the blood–brain barrier and therefore needs to be directly delivered to the brain. Ungerstedt et al. (1968) studied unilateral 6-OHDA lesions of the nigrostriatal pathway. By varying the position and extent of the lesion, different stages of human PD could be modeled. However, the 6-OHDA model has considerable limitations as well. It is a dopamine transporter-specific model and does not affect any other neurotransmitter.

Therefore, it does not replicate the full spectrum of clinical signs of human PD, i.e., the degeneration of the locus coeruleus with local depletion of norepinephrine is not replicated. In addition, the 6-OHDA-induced acute and local degeneration does not mirror the slow and extensive progression of neurodegeneration of the human disease. Finally, although lesioned animals show some of the cellular and behavioral deficits seen with the human disease, 6-OHDA-treated animals fail to develop Lewy bodies or α -synuclein-positive inclusions.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

In another model involving selective targeting of dopaminergic neurons in the brain, PD features are induced after administration of MPTP. The validity of the MPTP model is supported by the fact that MPTP exposure is a known, albeit rare, cause of drug-induced parkinsonism in humans (Davis et al. 1979; Langston et al. 1983). In mice, MPTP is typically administered systemically. MPTP is taken up primarily by astrocytes and converted to its metabolite MPP⁺. Then, it is taken up by dopaminergic neurons, where it exerts toxic effects. Interestingly, loss of dopaminergic neurons is observed not only in the basal ganglia but also in the enteric nervous system (Anderson et al. 2007). Varying regimens of MPTP delivery can produce varying degrees of nigrostriatal dysfunction. Acute dosing can produce lesions that result in mild to moderate cell loss, mimicking cell loss in early stages of human PD. Chronic dosing, consisting of long series of low-dose injections, results in more robust lesions representative of later stages of PD (Bezard et al. 1997). The MPTP mouse model has been invaluable in understanding the

Table 1 Pharmacological and toxicological models for Parkinson's disease

Molecule	Administration	Level of relevance	Target	I	MS	NMS	TH	BG	SP	Age	Ref
6-hydroxydopamine (6-OHDA)	Local	Derivate of dopamine	Causes oxidative stress after uptake by dopamine transporters	N	Y	NR	Y	Y	N	N	1
1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP)	Systemic	Known, albeit rare, cause of drug-induced parkinsonism in humans	Taken up by astrocytes primarily, converted to MPP ⁺ , which can be taken up by dopaminergic neurons, where it exerts toxic effects	Y	Y	Y	Y	Y	DD	Y	2
Rotenone	Systemic	Organic pesticide	Elicits mitochondrial dysfunction in a dopamine transporter independent fashion	Y	Y	NR	Y	Y	DD	NR	3
Paraquat, combined with maneb	Systemic	Paraquat is a pesticide, maneb is a fungicide	Causes redox cycling and thereby oxidative stress	Y	Y	NR	Y	Y	DD	NR	4

Age = age-related progression; BG = neurodegeneration in the basal ganglia; DD = dose-dependent; I = α -synuclein positive inclusions; MS = motor signs; N = no; NMS = nonmotor signs; NR = not reported; SP = slow progression; TH = reduced level of tyrosine hydroxylase; Y = yes

References (Ref): 1 = Ungerstedt et al. 1974; 2 = Anderson et al. 2007; Bezard et al. 1997; Davis et al. 1979; Irwin et al. 1992; Langston et al. 1983; 3 = Betarbet et al. 2000; p. 4 = Manning-Bog et al. 2002; Thiruchelvam et al. 2000

mechanisms underlying MPTP toxicity. However, despite robust replication of motor dysfunction and considerable preclinical successes in the screening for potentially therapeutic drugs, including coenzyme Q10, isradipine CR, and simvastatin (Beal et al. 1998; Ghosh et al. 2009; Meredith et al. 2008), the MPTP model has its limitations. For instance, mice may recover spontaneously after MPTP lesioning, thus hindering the assessment of therapeutic efficacy. The variability of MPTP sensitivity between distinct mouse strains and species is also problematic (Giovanni et al. 1994a, b; Sedelis et al. 2003). Studies on primates have demonstrated clear-cut parkinsonian features as well as protein aggregation after MPTP exposure. Consequently, this primate MPTP model has served as an adequate model for translational research toward the development and optimization of deep-brain stimulation therapies. In contrast, the MPTP model is less valid with other species, although as alluded above, the application of simvastatin in the MPTP mouse model produced interesting results in terms of protection against exotoxins (Ghosh et al. 2009).

Rotenone

The success of MPTP in replicating the neuropathology of human PD has led to the examination of other potential neurotoxin models for PD. Two promising models to emerge are the rotenone model and the combined paraquat/maneb model. Rotenone is an organic pesticide that inhibits complex I of the electron transport chain. It causes mitochondrial dysfunction and ultimately leads to cell loss in the nigrostriatal pathway (Betarbet et al. 2000). Rotenone can be delivered systemically via intranigral infusion or via gastric gavage to replicate human disease initiation in enteric neurons, as proposed by Braak (Braak et al. 2003). Rotenone exerts its effects in a dopamine transporter-independent fashion, thereby eliciting mitochondrial dysfunction in nondopaminergic systems as well. Nevertheless, its neurotoxic effects are predominantly dopamine neuron-selective. Data from cell culture experiments suggest that rotenone triggers intracellular dopamine release, which could in turn explain the toxic effect on dopaminergic neurons (Inden et al. 2011). However, the variability of sensitivity between individuals and species and the potential of this toxin to induce widespread systemic toxicity (Ravenstijn et al. 2008) complicates the use of the rotenone model for translational research.

Paraquat/maneb

Paraquat is a pesticide that is first converted to a cation before being reoxidized. This reaction produces superoxide radicals, which in turn cause further redox cycling and

oxidative stress. Paraquat is frequently administered in combination with maneb, a fungicide that has been linked to the development of parkinsonian symptoms in humans (Thiruchelvam et al. 2000). Exposure of rodents to a combination of paraquat and maneb results in significant nigral cell loss and nigral α -synuclein-positive inclusions. Rats prenatally exposed to maneb show increased sensitivity to paraquat toxicity in adulthood. These observations support the multihit hypothesis of PD, which suggests that early insults can sensitize the nigrostriatal system to subsequent hits in adulthood (Thiruchelvam et al. 2000).

Trichloroethylene

Trichloroethylene (TCE), a solvent widely used as a degreasing agent, is also considered an environmental risk factor for PD (Gash et al. 2008; Goldman 2010). Peritoneal administration of TCE causes dopaminergic neuronal cell death in mice (Guehl et al. 1999). In rats, oral administration of TCE induces key features of PD, i.e., loss of nigral dopaminergic neurons, reduced mitochondrial complex I activity, oxidative stress, microglial activation, and α -synuclein accumulation (Liu et al. 2010a, b). However, the relevance of this model for translational research remains to be evaluated.

Overall, pharmacological and neurotoxic models help to understand the consequences of striatal dopamine loss and to develop current dopaminergic therapies (Bove et al. 2005). A major limitation of toxin-induced models, however, is that they do not reproduce the complete spectrum of human pathology. Although they are excellent for evaluating the role of the nigrostriatal system in PD and may be adequate for testing restorative therapeutic compounds, most of these models are limited in their ability to replicate important aspects of human PD such as its progressive nature and Lewy body formation.

Genetic models for PD

In the last decade, considerable advances have been made in the identification of genes responsible for monogenic familial PD. Since 1998, 14 different genes have been identified to cause familial PD (Schapira 2006; Schapira and Tolosa 2010). In addition, recent genome-wide association studies (GWAS) led to the identification of yet another set of risk-associated genes. Besides its role in familial PD, α -synuclein is, worldwide, the most common risk factor for idiopathic PD (Pankratz et al. 2009; Satake et al. 2009). Strong association signals were also identified at the *MAPT* and *LRRK2* loci (Simon-Sanchez et al. 2009). Other important risk factors for PD are mutations in the glucocerebrosidase gene (Sidransky et al. 2009). A more

recently identified risk factor for PD, named PARK16, is associated with reduced risk for PD (Tan et al. 2010). Most recently, five additional PD risk factors have been reported: ACMSD, STK39, MCCC1/LAMP3, SYT11, and CCDC62/HIP1R (International Parkinson Disease Genomic Consortium 2011). As PD appears to be a complex genetic disease sensitive to environmental factors, the discovery of genetic factors in PD led to a new generation of PD models: the genetic PD mouse models.

α -Synuclein models

The very first identified mutations leading to familial PD were located in the gene encoding α -synuclein (Chartier-Harlin et al. 2004; Ibanez et al. 2004; Kruger et al. 1998; Polymeropoulos et al. 1997). In addition to single nucleotide polymorphisms (SNPs), rare triplications and duplications of the α -synuclein gene (*SNCA*) were reported in human PD (Ahn et al. 2008; Gasser 2009b; Singleton et al. 2003). However, α -synuclein, which typically accumulates in Lewy bodies (Spillantini et al. 1998), is not mutated in the large majority of PD patients. Nevertheless, numerous lines of mice overexpressing α -synuclein have been generated using distinct promoters and transgenes (Fernagut and Chesselet 2004). These models use transgenes with mutations causing familial PD, the full-length protein, or truncated forms of the protein. Most recapitulate some but not all aspects of PD, and effects relevant to the disease are generally correlated to the levels of α -synuclein expression (Magen and Chesselet 2010). Importantly, expression of transgenes is not limited to dopaminergic neurons but is defined by the nature of the genetic modification, i.e., promoter and genomic insertion site. However, a common advantage of these models, compared to pharmacological and toxicological models, is the slowly progressive accumulation of α -synuclein, a typical feature of idiopathic PD. The main strength of α -synuclein models is the ability to replicate α -synuclein-positive inclusions (Table 2), although the typical fibrillar halo structure of Lewy bodies, observed in human PD, is not observed in the murine α -synuclein-positive inclusions (Maries et al. 2003). A major limitation of α -synuclein models is their inability to model cell loss in the substantia nigra pars compacta. Mice overexpressing wild-type human α -synuclein exhibit reduced olfaction, autonomic dysfunction, α -synuclein accumulation, and early motor deficits in the absence of nigrostriatal neurodegeneration (Chesselet et al. 2008; Fleming et al. 2004; Fleming et al. 2008; Rockenstein et al. 2002).

α -Synuclein knockout mice are viable and show decreased striatal dopamine levels and reduced rearing. These findings may be explained by the hypothesis that α -synuclein plays a role in synaptic vesicle function. Triple

$\alpha\beta\gamma$ -synuclein knockout mice present age-dependent synaptic and neuronal dysfunction, demonstrating that synucleins contribute to the long-term operation of the nervous system (Burre et al. 2010; Greten-Harrison et al. 2010). Conversely, mice overexpressing α -synuclein develop intraneuronal inclusions and show decreased striatal dopamine levels, despite lacking nigral cell loss. However, mice overexpressing a double-mutated or a truncated form of α -synuclein under the tyrosine hydroxylase (TH) promoter present a selective loss of nigrostriatal dopaminergic neurons. The double-mutated α -synuclein variant (A30P/A53T) used in one of these studies has never been described in humans (Thiruchelvam et al. 2004). In contrast, expression of N-terminal α -synuclein fragments, comparable to those used in the second study (Wakamatsu et al. 2008a), has been detected in PD brain extracts (Li et al. 2005). In addition, the relevance of the A53T mutation in mouse models remains to be evaluated. Although the A53T mutation can cause PD in humans, threonine is the wild-type residue at this position in the murine sequence (Cabin et al. 2005; Larsen et al. 2009). Human A53T α -synuclein, however, was described to be more toxic on an α -synuclein-null background than on a murine wild-type background. This contrast between the protective effects of wild-type mouse α -synuclein and the deteriorative effects of human A53T α -synuclein on mice might be linked to the six other α -synuclein amino acid differences between these two species (Cabin et al. 2005).

Recently, data from tyrosine hydroxylase (TH) promoter-controlled α -synuclein-overexpressing mouse models led to the hypothesis that microglial activation is an early hallmark of PD (Su et al. 2008, 2009). Findings at the neurochemical and gene expression level suggest that α -synuclein also influences dopamine metabolism (Miller et al. 2007; Richfield et al. 2002; Yu et al. 2008). In addition, TH promoter-controlled overexpression of the double-mutated α -synuclein impairs the ubiquitin proteasome system in aged mice (Chen et al. 2006). The main limitation of this model is a spatially restricted pathology. This limitation can be circumvented, at least in part, by crossing α -synuclein transgenic mice with mice lacking murine α -synuclein. In this case, the absence of endogenous α -synuclein appears to drive the aggregation of transgenic α -synuclein throughout different brain regions (Prasad et al. 2011). In contrast, human Lewy body formation and α -synuclein expression in neurites are widely distributed in both the central and peripheral nervous systems (Braak et al. 2003; Halliday et al. 2005).

Platelet-derived growth factor- β (PDGF- β) promoter-controlled α -synuclein-overexpressing mouse models aim to mimic the broad distribution of α -synuclein pathology in humans (Masliah et al. 2000). Recent findings suggest that overexpression of A53T α -synuclein affects neurogenesis

Table 2 Alpha-synuclein models

Model(s)	Promoter	Background	I	MS	NMS	TH	BG	SP	Age	Ref
WT, A53T	PDGF- β	C57BL/6 \times DBA2	Y	Y	NR	Y	Y	NR	Y	1
WT	KO	C57BL/6	NR	NR	NR	NR	NR	NR	NR	2
WT	PDGF- β	C57BL/6	NR	NR	NR	NR	NR	Y	NR	3
A53T	Mouse Thy-1	C57BL/6	LN	Y	NR	NR	N	NR	NR	4
WT, A30P, A53T	Mouse Thy-1	C57BL/6	Y	Y	IFC	NR	Y	NR	Y	5
<u>WT</u> , (A30P)	Mouse Thy-1	C57BL/6 \times DBA2	Y	Y	Y	Y	Y	Y	N	6
<u>Y39C</u>	Mouse Thy-1	FVB/N	Y	Y	CD	N	N	Y	Y	7
A30P + A53T	Human Thy-1	C57BL/6 \times DBA2	Y	Y	N	Y	Y	Y	N	8
(WT), (A30P), <u>A53T</u>	Mouse prion	C3H/HeJ \times C57BL/6J backcrossed into C57BL/6J <i>PARKIN</i> KO	Y	Y	MD	N	Y	N	Y	9
WT, <u>A53T</u>	Mouse prion	C57BL/6 \times C3H	Y	Y	RA	N	Y	Y	N	10
(WT), <u>A53T</u>	Mouse prion	FVB/N, FVB \times 129, α -synuclein KO	N	Y	NR	NR	NR	Y	N	11
(WT), <u>A30P</u>	Mouse prion	C57BL/6J \times DBA2 backcrossed into C57BL/6J	N	Y	ASP	N	NR	NR	Y	12
WT, <u>A30P</u> , A53T	Hamster prion	C57BL/6J \times SJL	N	Y	NR	N	NR	Y	Y	13
WT, A30P, A53T	Rat THP	Swiss Webster \times C57BL/DBA	N	NR	NR	N	NR	NR	NR	14
WT, <u>A30P</u> \pm <u>A53T</u>	Rat THP	C57BL/6J	N	Y	NR	NR	NR	Y	Y	15
Truncated (1-120)	Rat THP	C57BL/6J \times CBA/ca backcrossed into C57BL/6J, α -synuclein KO	Y	Y	NR	NR	N	Y	Y	16
Truncated (1-130)	Rat THP	C57BL/6J	N	N	REB	Y	Y	N	N	17
A30P + A53T	Chicken beta actin, BA	C57BL/6	NR	NR	MD	N	N	NR	Y	18
A30P + A53T	Mouse THP	C57BL/6	NR	NR	MD	N	N	NR	Y	19
A30P + A53T	Mouse prion	C57BL/6	NR	NR	NR	NR	N	NR	NR	20
WT, A30P, A53T	CaM-tTA (tet-off)	C57BL/6 (WT and A30P), C57BL/CH3 (WT and A53T)	N	Y	CD	NR	Y	Y	Y	21
A30P	KI in endogenous α -synuclein	C57BL/6	NR	Y	NR	RD	NR	Y	Y	22
Truncated (1-119)	Conditional ROSA26	C57BL/6J	N	NR	NR	RD	N	NR	N	23
A53T	Conditional ROSA26	C57BL/6J	N	NR	NR	NR	N	NR	N	23
WT, A30P, A53T	Endogenous α -synuclein (BAC)	FVB/N \times 129S6/SvEvTac	N	Y	Y	NS	N	Y	N	24

Alpha-synuclein models express truncated or full-length α -synuclein with or without mutations. The expression of these constructs, in different mouse strains, is controlled by different promoters and causes distinct phenotypes. The models are grouped by project. *Lines* with a stronger phenotype are *underlined* and *lines* without phenotype are in *parentheses*

Age = age-related progression; ASP = affected synaptic plasticity; BA = beta-actin promoter; BG = neurodegeneration in the basal ganglia; CD = cognitive deficits; I = α -synuclein positive inclusions; IFC = impaired fear conditioning; LN = Lewy-like neurites; MD = mitochondrial deficits; MS = motor signs; N = no; NMS = nonmotor signs; NR = not reported; NS = not significant; RA = reduced anxiety; RD = reduced dopamine level; REB = reduced exploratory behavior; SP = slow progression; TH = reduced level of tyrosine hydroxylase; THP = tyrosine hydroxylase promoter; Y = yes

References (Ref): 1 = Hashimoto et al. 2003; Koob et al. 2010; Maslah et al. 2000; Rockenstein et al. 2002; Winner et al. 2004; Winner et al. 2008; Yacoubian et al. 2008; 2 = Sharon et al. 2003; 3 = Liu P et al. Liu et al. 2010a, b; 4 = van der Putten et al. 2000; 5 = Frasier et al. 2005; Freichel et al. 2007; Kahle et al. 2000; Neumann et al. 2002; Poon et al. 2005; Schell et al. 2009; 6 = Fernagut et al. 2007; Fleming et al. 2004; Fleming et al. 2006; Fleming et al. 2008; Koob et al. 2010; Rockenstein et al. 2002; Song et al. 2004; Wang et al. 2008; Watson et al. 2009; Wu et al. 2010; 7 = Zhou et al. 2008; 8 = Ikeda et al. 2009; Ono et al. 2009; 9 = Lee et al. 2002; Martin et al. 2006; Miller et al. 2007; Unger et al. 2006; von Coelln et al. 2006; 10 = Gao et al. 2008; George et al. 2008; Giasson et al. 2002; Graham and Sidhu 2010; Norris et al. 2007; Sotiriou et al. 2010; 11 = Cabin et al. 2005; Gispert et al. 2003; 12 = Gureviciene et al. 2007; 2009; Oksman et al. 2009; Yavich et al. 2006; Yavich et al. 2005; 13 = Gomez-Isla et al. 2003; Nieto et al. 2006; 14 = Manning-Bog et al. 2003; Matsuoka et al. 2001; Yu et al. 2008; 15 = Chen et al. 2006; Miller et al. 2007; Richfield et al. 2002; Su et al. 2009; Su et al. 2008; Thiruchelvam et al. 2004; 16 = Tofaris et al. 2006; 17 = Wakamatsu et al. 2008a; Wakamatsu et al. 2008b; 18 = Maskri et al. 2004; Stichel et al. 2007; 19 = Maskri et al. 2004; Stichel et al. 2007; 20 = Maskri et al. 2004; 21 = Lim et al. 2010; Marxreiter et al. 2009; Nuber et al. 2008; 22 = Plaas et al. 2008; 23 = Daher et al. 2009; 24 = Kuo et al. 2010

and proliferation of newly born neurons in the subventricular zone (Winner et al. 2004, 2008). Molecular analysis of mice with PDGF- β -controlled overexpression of α -synuclein suggested that interactions between α -synuclein, polyunsaturated fatty acids, and cholesterol accelerate α -synuclein aggregation (Bieschke et al. 2006; Sharon et al. 2003). Koob et al. (2010) used this model to show that treatment with the cholesterol synthesis inhibitor lovastatin alleviates these alterations. In PDGF- β / α -synuclein mice, gene expression is altered. However, neuronal death has not yet been reported in these mice (Yacoubian et al. 2008). Changes due to overexpression of α -synuclein are restricted mainly to the olfactory bulb and the hippocampus, and deficits occur relatively late. Despite changes at the gene expression level, dopamine metabolism, TH terminals, and neurogenesis, no overt pathology of the nigrostriatal system or clinical hallmarks have been observed in PDGF- β / α -synuclein mice.

In contrast to PDGF- β / α -synuclein models, prion protein promoter α -synuclein models aim to study the effects of extremely high overexpression of α -synuclein in neurons usually involved in PD, including neurons of the substantia nigra (Maskri et al. 2004). However, the translational relevance of these models, with typically severe motor deficits, is mitigated by high transgene expression in motor neurons of the spinal cord and brainstem, which confer behavioral deficits that are not characteristic for PD (Magen and Chesselet 2010). An additional drawback is the lack of cell loss in the substantia nigra and locus coeruleus.

Compared to the prion protein promoter, the Thy-1 promoter causes a more widespread expression of α -synuclein, which is not restricted to catecholaminergic neurons (Rockenstein et al. 2002), and does not cause any motor neuron loss when used in C57BL/6 mice. Nigral cell loss was observed in only a few cases, but most of the studies found typical PD phenotypes such as loss of dopamine in the striatum, motor deficits, and nonmotor deficits (Fleming et al. 2004; Ikeda et al. 2009; Ono et al. 2009; van der Putten et al. 2000). These mice further develop an age-dependent neurite terminal α -synuclein pathology, suggesting that α -synuclein is selectively phosphorylated in restricted brain regions (Schell et al. 2009). Some Thy1/ α -synuclein mouse lines present early motor and nonmotor deficits equivalent to those in PD prior to clinical diagnosis, suggesting that these models could be useful for the study of preclinical PD stages and hence for translational research (Fernagut et al. 2007; Fleming et al. 2004, 2006, 2008; Koob et al. 2010; Song et al. 2004). However, other studies using Thy1/ α -synuclein mouse lines demonstrated a much later onset, or even absence, of motor dysfunction (Freichel et al. 2007; Neumann et al. 2002; Zhou et al. 2008).

Models overexpressing α -synuclein under the calcium/calmodulin-dependent protein kinase II α (CaM) promoter were initially designed to study postnatal neurogenesis in the olfactory bulb and hippocampus. Conditional overexpression driven by the CaM promoter can be triggered by a tetracycline transactivator. The emergence of conditional transgenic models enables detailed investigation of the reversibility of α -synuclein pathology, thereby helping to focus on therapeutic strategies that aim to regulate α -synuclein expression at early stages of the disease (Lim et al. 2010; Marxreiter et al. 2009; Nuber et al. 2008). Recent models allow the control of gene expression in a region-dependent manner. One example is the Cre/loxP-based mouse model—expressing truncated N-terminal α -synuclein fragments—that shows reduced striatal dopamine levels but no neurodegeneration (Daher et al. 2009).

The most recently reported α -synuclein mouse model expresses A53T α -synuclein under a P1 artificial chromosome on an α -synuclein-null background. These mice have early motor deficits but no α -synuclein-positive inclusions, no loss of TH-positive cells in the substantia nigra, and no dopamine loss in the striatum. However, these mice have decreased colonic motility that may result from proteinase K-resistant α -synuclein aggregates found in neurons of the enteric nervous system. Olfactory function and cardiac innervation remain intact (Kuo et al. 2010). Consistently, this model could serve to investigate therapies for gastrointestinal dysfunction in early preclinical PD stages.

PARKIN, PTEN-induced putative kinase 1 (PINK1), and DJ1

In addition to the α -synuclein model, other models of familial PD have been reported. Recessive mutations in *PARKIN*, *PINK1*, and *DJ1* were mostly modeled using knockout strategies that result in the lack of the corresponding protein and, so far, to modest PD-associated deficits (Table 3).

The most frequent mutations causing early-onset recessive familial forms of PD occur in the *PARKIN* gene. *PARKIN* is an ubiquitin E3 ligase that ubiquitinates proteins to regulate a variety of cellular processes. Loss of E3 ligase activity is thought to play a pathogenic role in both inherited and sporadic PD (Dawson and Dawson 2010). More recently, *PARKIN* has been demonstrated to play a role in maintaining mitochondrial homeostasis through targeting damaged mitochondria for mitophagy (Tanaka 2010). *PARKIN* loss-of-function could thus lead to enhanced presence of dysfunctional mitochondria, a process that could contribute to PD pathogenesis. *PARKIN* knockout mice have been generated by deleting either exon 3 or 7. These lines show mild, progressive motor deficits and premotor signs typical of PD, i.e., reduced dopamine

Table 3 Summary of genetic PD perturbations and available genetic PD mouse models

Association with PD	Loci	Gene	Genotype(s) of mouse models	Promoter type	Background	I	MS	NMS	TH	BG	SP	Age	Ref
Common	PARK1 and 4	<i>SNCA</i>	Table 2 (T2)	T2	T2	T2	T2	T2	T2	T2	T2	T2	T2
Common	PARK2	<i>PARKIN</i>	Deletion of exon 7 causing a frame shift and premature termination	KO	Protamine-Cre mice (129/SvJae × (BALB/c × C57BL/6 F1)) × C57BL/6	NR	N	Y	Y	Y	N	N	1
Common	PARK2	<i>PARKIN</i>	<i>PARKIN</i> interrupted within exon 3	KO	129SV	N	Y	Y	N	NR	NR	NR	2
Common	PARK2	<i>PARKIN</i>	Deletion of exon 3	KO	C57BL/6J × 129/Sv	NR	N	Y	N	NR	NR	NR	3
Common	PARK2	<i>PARKIN</i>	Q311X	BAC	FvB	NR	Y	NR	Y	Y	Y	Y	4
Common	PARK2	<i>PARKIN</i>	Most of exon 3 was replaced with EGFP + stop	KO	C57BL/6J × 129/Sv	NR	Y	NR	N	NR	Y	Y	5
Common	PARK2	<i>PARKIN</i>	Exon 3 deletion (PaKO)	KO	129SvJ backcrossed into C57BL/6	NR	NR	MD	N	N	NR	Y	6
Common, combination	PARK2	<i>PARKIN</i>	Double mutant with <i>PARKIN</i> deletion (PaKO) and overexpression of A30P + A53T α -synuclein driven by BA	KO + B A- α -synuclein	129SvJ × C57BL/6	NR	NR	MD	N	N	NR	Y	7
Common, combination	PARK2	<i>PARKIN</i>	Double mutant with <i>PARKIN</i> deletion (PaKO) and overexpression of A30P + A53T α -synuclein driven by THP	KO + TH- α -synuclein	129SvJ × C57BL/6	NR	NR	MD	N	N	NR	Y	7
Common	PARK6	<i>PINK1</i>	Most of exon 2, and exons 3-5 were replaced by IRES-lacZ/MC1neo	KO	129SvEvBrd × C57BL/6J	NR	NR	HSN	N	NR	NR	NR	8
Common	PARK6	<i>PINK1</i>	Deletion of exons 4-7	<i>PINK1</i> -1 null allele	C57BL/6 × 129/Sv	NR	NR	MD	N	N	NR	Y	9
Common	PARK6	<i>PINK1</i>	G309D	HR	129/SvEv	N	Y	MD	N	N	Y	Y	10
Common	PARK7	<i>DJI</i>	Premature stop codon in exon 2	KO	C57BL/6	N	N	NR	N	NR	NR	N	11
Common	PARK7	<i>DJI</i>	Deletion of a promoter subregion and the first 5 exons	Null allele	129 × C57BL/6J, E14Tg2A.4	N	Y	DD	N	NR	NR	Y	12
Common	PARK8	<i>LRRK2</i>	R1441G	BAC	FvB	NR	Y	DD	Y	NR	Y	Y	13
Common	PARK8	<i>LRRK2</i>	R1441C	KI	B6/129	N	MH	DD	N	NR	NR	NR	14
Common	PARK9	<i>ATP13A2</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15
Common	Combination	<i>PARKIN</i> + <i>PINK1</i> + <i>DJI</i>	Triple KO	KO	C57BL/6 × 129/Sv	NR	NR	NR	N	N	NR	N	16

Table 3 continued

Association with PD	Loci	Gene	Genotype(s) of mouse models	Promoter type	Background	I	MS	NMS	TH	BG	SP	Age	Ref
Rare	PARK3	Unknown	SPR is a candidate gene for PARK3. The 2 first SPR exons are replaced with a lacZ-neomycin cassette	KO	C57BL/6J-Tyrc-Brd × 129S5/SvEvBrd	NR	Y	NR	Y	NR	NR	Y	17
Rare	PARK5	<i>UCHL1</i>	WT, 193 M. In addition, overexpression of α -synuclein was triggered via adenovirus.	PDGF- β	C57BL/6	NR	NR	NR	Y	Y	NR	NR	18
Rare	PARK11	<i>GIGYF2</i>	<i>GIGYF2</i> \pm <i>GIGYF2</i> ^{-/-}	Gene trap	C57BL/6 × Tyr ^{c-Brd} /129Ola	Y	Y	NR	NR	Y	NR	Y	19
Rare	PARK13	<i>HTRA2</i>	Exons 2-6, and parts of exons 1 + 7 are replaced by the PGK-neo gene	KO	C57BL6/J	NR	Y	NR	Y	Y	N	N	20
Rare	PARK13	<i>HTRA2</i>	<i>HTRA2</i>	NSE	FVB/N	NR	NR	NR	NR	NR	NR	NR	21
Rare	PARK14	<i>PLAG6</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	22
Risk factor	PARK10	<i>AAOPD</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	23
Risk factor	PARK12	Unknown	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	24
Risk factor	PARK15	<i>FBXO7</i>	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	25
Risk factor	PARK16	Unknown	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	26

The listed risk factors are restricted to PARK loci recently identified by means of genome-wide association studies (GWAS). Despite the lack of adequate models for some of these factors, the published mouse models cover the majority of the known genetic factors for PD

Age = age-related progression; BA = beta-actin promoter; BG = neurodegeneration in the basal ganglia; DD = dopaminergic dysfunction; HR = homologous recombination; HSN = hyperexcitable substantia nigra neurons; I = α -synuclein positive inclusions; MD = mitochondrial deficits; MH = only under multiple hits; MS = motor signs; N = no; NA = not available; NMS = nonmotor signs; NR = not reported; NSE = rat neuron-specific enolase promoter; SP = slow progression; TH = reduced level of tyrosine hydroxylase; THP = tyrosine hydroxylase promoter; Y = yes

References (Ref): 1 = O'Gorman et al. 1997; Von Coelln et al. 2004; 2 = Itier et al. 2003; Menendez et al. 2006; Periquet et al. 2005; Rodriguez-Navarro et al. 2007; 3 = Zhu et al. 2007; 4 = Lu et al. 2009; 5 = Goldberg et al. 2003; Martella et al. 2009; Palacino et al. 2004; 6 = Stichel et al. 2007; 7 = Stichel et al. 2010; Wood-Kaczmar et al. 2008; 9 = Gautier et al. 2008; Kitada et al. 2007; Martella et al. 2009; 10 = Gispert et al. 2009; 11 = Kim et al. 2005; 12 = Kim et al. 2009; 13 = Li et al. 2009; 14 = Tong et al. 2009; 15 = Ramirez et al. 2006; 16 = Kitada et al. 2009; 17 = Takazawa et al. 2008; 18 = Setsuie et al. 2009; 19 = Giovannone et al. 2009; 20 = Bishop et al. 2010; Martins et al. 2004; 21 = Liu et al. 2007; 22 = Yoshino et al. 2010; 23 = Haugarvoll et al. 2009; Li et al. 2007; 24 = Pankratz et al. 2003; 25 = Di Fonzo et al. 2009; Paisan-Ruiz et al. 2010; 26 = Satake et al. 2009; Simon-Sanchez et al. 2009; Tan et al. 2010

release, synaptic anomalies, mitochondrial damage, and increased oxidative stress. However, none of these models shows a progressive loss of nigrostriatal dopaminergic neurons (Goldberg et al. 2003; Itier et al. 2003; Martella et al. 2009; Palacino et al. 2004; Periquet et al. 2005; Rodriguez-Navarro et al. 2007; Stichel et al. 2007; Von Coelln et al. 2004; Zhu et al. 2007). Dopaminergic cell loss can be induced by exposure to the inflammatory stressor lipopolysaccharide (LPS) (Frank-Cannon et al. 2008), illustrating that *PARKIN* mutations may make dopaminergic neurons more vulnerable to environmental insults. Lu et al. (2009) investigated whether the *PARKIN* mutation Q311X exerts dominant toxicity on nigrostriatal dopaminergic neurons. The selective expression of this mutation in dopaminergic neurons does indeed cause progressive nigrostriatal dopaminergic cell loss, α -synuclein pathology, and motor deficits (Lu et al. 2009). This implies that these mice provide a model for dopaminergic neuron death caused by *PARKIN* mutations.

Similar to *PARKIN* knockout mice, *PINK1* and *DJI* mice have, so far, failed to reproduce canonical PD deficits. Similar observations were made in a triple transgenic model lacking *PARKIN*, *PINK1*, and *DJI* (Kitada et al. 2009). Without additional insults, *PINK1* and *DJI* deficiency does not cause spontaneous loss of nigrostriatal dopaminergic neurons (Aron et al. 2010; Morais et al. 2009). However, most of these mice show reduced activity, increased oxidative stress, and increased vulnerability to mitochondrial toxins (Chen et al. 2005; Gautier et al. 2008; Gispert et al. 2009; Kim et al. 2005). Overall, recessive PD models appear to have potential for the modeling of environmental factors in familial forms of PD.

Leucine-rich repeat kinase 2 (LRRK2)

Dominant *LRRK2* mutations have recently been identified as causes of familial PD. Heterozygote carriers can develop familial PD with characteristics similar to the sporadic disease forms (Cookson et al. 2008). However, penetrance is strongly age-dependent. At the age of 69 years, only 51% of carriers show signs of PD (Healy et al. 2008). Several mutations have been identified in human PD patients, the most frequent one being the G2019S mutation. Lin et al. (2009) generated *LRRK2* knockout mice and transgenic mice with inducible overexpression of the human wild-type, the G2019S mutant, or the kinase domain-deleted *LRRK2*. Neither deletion nor overexpression of these *LRRK2* constructs caused gross neurodegeneration. However, all three *LRRK2* constructs exacerbated the progression of human A53T α -synuclein-induced neuropathology. Overexpression of *LRRK2* or its mutants impaired the structure and function of the Golgi complex

and microtubule-based transport, resulting in a pathogenic somatic accumulation of α -synuclein (Lin et al. 2009).

Later, Li et al. (2010) characterized two bacterial artificial chromosome (BAC) transgenic mouse strains overexpressing either wild-type or G2019S-mutated *LRRK2*. Transgenic mice overexpressing wild-type *LRRK2* presented an elevated striatal dopamine release, were hyperactive, and showed enhanced motor performance. In contrast, mice expressing the G2019S mutant showed an age-dependent decrease in striatal dopamine content (Li et al. 2010). Melrose et al. (2010) also reported impaired dopaminergic neurotransmission in BAC *LRRK2* mice. In G2019S mice, these changes were linked to a modified localization and phosphorylation of the microtubule-binding protein tau (Melrose et al. 2010). A more recent study that also used mice that overexpress G2019S *LRRK2* by using a BAC construct, analyzed adult neurogenesis (Winner et al. 2011). The proliferation and survival of newly generated cells was significantly decreased by the overexpression of G2019S *LRRK2*, and newly generated neurons exhibited reduced dendritic arborization and fewer spines (Winner et al. 2011).

Mice harboring the R1441G mutation develop a strong behavioral phenotype and an altered dopamine release (Li et al. 2009). In contrast, mice harboring the R1441C mutation do not present prominent motor defects but only dopaminergic deficits (Tong et al. 2009). *LRRK2* seems to be involved in both familial and idiopathic PD. Therefore, *LRRK2* is a very attractive target for therapeutic intervention (Paisan-Ruiz et al. 2004; Satake et al. 2009; Simon-Sanchez et al. 2009; Zimprich et al. 2004). The value of *LRRK2* mouse models for translational research in this direction remains to be evaluated, but primary results indicate that these models might be useful for analyzing impaired cellular dynamics that cause dopaminergic dysfunction.

Models for other network perturbations in PD

Genetic models of PD are widely used. However, only a few of these models reproduce the cardinal features of the disease. Most strikingly, most genetically altered mice do not show extensive or progressive loss of nigrostriatal dopaminergic neurons (Chesselet et al. 2008). It is reasonable to assume that distinct causal factors leading to neurodegeneration in PD perturb converging molecular or cellular pathways. In fact, the concept of PD as network perturbation might be useful to guide translational research (Del Sol et al. 2010). Consequently, models for network perturbations are relevant to translational research in PD. These include the above-mentioned genetic and toxic models as well as models for genetic risk factors and

models for disease pathway perturbations such as mitochondrial dysfunction (Wellstead and Cloutier 2011).

Aphakia and weaver mice

Besides blindness, the so-called aphakia mice—lacking the transcription factor *Pitx3*—present complete loss of nigrostriatal dopaminergic neurons during early postnatal development. This model does not clearly reproduce progressive loss of dopaminergic neurons in PD, yet it is useful to validate behavioral mouse tests for dopaminergic deficits (Hwang et al. 2005). *Pitx3* polymorphisms have been associated with an increased risk for PD (Haubenberg et al. 2011) and may therefore be involved in human PD. In addition, *Pitx3* may directly regulate expression of the vesicular monoamine transporter (*VMAT*) and the dopamine transporter (*DAT*), two genes associated with increased risk for PD (Hwang et al. 2009; Ritz et al. 2009; Takahashi et al. 1997).

In turn, weaver mutants carry a mutation in the G-protein-coupled inwardly rectifying channel (*GIRK2*) (Guatteo et al. 2004). An important characteristic of these mice for research in PD is a gradual nigrostriatal dopaminergic neurodegeneration (Cavalcanti-Kwiatkoski et al. 2010).

VMAT

Mice with reduced expression of VMAT, member 2 (*VMAT2*) have reduced monoamine storage capacity and present both a progressive loss of striatal dopamine and L-DOPA-responsive motor deficits. In addition, *VMAT2*-deficient mice present progressive nonmotor signs such as progressive deficits in olfactory discrimination, delayed gastric emptying, altered sleep latency, and age-dependent depressive behavior. This model might be valuable for translational research toward restoration of monoamine dysfunction at early nonmotor stages of PD (Taylor et al. 2009).

MitoPark mice

The so-called MitoPark mouse—lacking the mitochondrial transcription factor A (TFAM)—is a model of mitochondrial dysfunction in dopaminergic midbrain neurons. These mice exhibit an adult-onset progressive loss of nigrostriatal dopaminergic neurons, accompanied by the formation of intraneuronal inclusions (Ekstrand and Galter 2009; Ekstrand et al. 2007). As in human PD, impaired nigrostriatal function precedes the onset of motor deficits, and L-DOPA administration improves motor dysfunction (Galter et al. 2010; Good et al. 2011). MitoPark mice may provide a useful model for investigating neuroprotective strategies (Harvey et al. 2008). However, is it not yet fully

understood whether mitochondrial dysfunction is the cause of PD or whether it is a consequence of other perturbations within a cascade of pathogenic events.

Aging

Aging is the primary risk factor for the development of PD. In fact, there are many parallels between normal aging and early stages of PD. In normal aging, the striatal dopamine levels are reduced and there is loss of dopaminergic nigral neurons. These losses are associated with age-related increases in α -synuclein (Irwin et al. 1992; McNeill and Koek 1990). Collectively, these findings suggest that aged animals represent a useful model for the evaluation of therapies aimed at the earliest stages of PD and that it might be valuable to rethink aged animals' validity for translational research in PD.

Future challenges and needs in PD animal models and translational research

Today, we understand that the prodrome of PD can be initiated by genetic and environmental factors. However, the total number of involved genes is not yet known. In addition, different genetic backgrounds, for instance, between different consomic mouse strains, can influence the phenotypic outcome in animal models (Nishi et al. 2010). One challenge is, therefore, to better understand the complex relationships between genetic factors and PD onset and manifestation. One possibility is to identify regions of the genome that play a role in complex PD-related traits. In the case of PD, quantitative trait loci (QTLs) could be used to map the genes underlying parkinsonian phenotypes or susceptibility to PD. The Complex Trait Consortium has provided a reference panel of recombinant inbred strains designed for QTL analysis (Churchill et al. 2004; Vogel 2003). These congenic mouse strains, generated by mating distinct inbred strains and backcrossing the descendants, harbor nearly identical genomes. The resulting set of populations allows the analysis of the effects of different genetic backgrounds. The already existing genetic PD mouse models, in contrast, are designed to analyze the role of isolated genetic loci on a fixed background. Recently, GWAS aimed to better understand the genetic basis underlying PD. Both QTL analysis and whole-genome sequencing are powerful complementary tools for proceeding with these studies.

Future therapeutic interventions will likely aim at interrupting the progression of molecular and pathological prodromes. However, the causal cascade of pathogenic events is not yet fully understood. To improve the understanding of early pathogenesis, it will be necessary to

analyze the temporal and causal coupling between events at the molecular, cellular, and organism scales. Furthermore, the history of translational research in well-studied diseases (e.g., Alzheimer disease) has demonstrated that findings from mouse models may not always be extrapolated to humans (Van Dam and De Deyn 2011). The validity of animal models of human diseases will therefore need to be evaluated. Of great importance, biomarkers found in animal models might help improve clinical risk evaluation and early diagnosis. Furthermore, biomarkers will allow us to empirically choose the most adequate animal models for specific questions in translational research (Srivastava et al. 2010). Novel techniques like live cell imaging and nano-surgery in the living mouse brain (Mascaro et al. 2010), progress in the development of epigenetic analysis tools, and reduced costs for omics analysis will help in the investigation of the complexity underlying PD. The complex relationships between multiple scales and evaluation of model relevance for clinical research will require new tools for the analysis of complex biological systems, i.e., systems biology, computational biology, and interdisciplinary cooperation. These tools should be suitable for developing translational research into a predictive, preventive, personalized, and participatory medicine (Auffray et al. 2010). An important step on the way to achieve personalized medicine will be to rank the potential of therapeutic strategies per disease state. In addition to mouse models, other animal models, including other rodents, primates, *Drosophila melanogaster*, *Caenorhabditis elegans*, and *Saccharomyces cerevisiae* (Hirth 2010; Nass et al. 2008; Witt and Flower 2006) as well as cellular models, should be considered. The adequate choice of models is critical for the outcome of translational research.

Conclusion

It is broadly accepted that current PD mouse models do not adequately present typical sets of symptoms characteristic of human PD. The striking differences between brain size and complexity between rodents and humans limit the direct translation of the experimental results to the clinic. Model and species properties determine the characteristics of the syndrome. Full reproduction of neuropathological and clinical PD manifestations is not expected in the mouse. However, a useful model should at least be of mechanistic relevance, thereby allowing potential therapeutic testing. The awareness that many mouse models show premotor symptoms of PD raises the possibility of development of novel treatments. However, none of the available models accurately recapitulates the complex and progressive pathology that characterizes human PD. These important shortcomings must be taken into account when

translating information from the laboratory to the clinic. However, it is too simple to argue that the lack of reliable models for preclinical testing undermines investigations in clinical trials. An appropriate model should be chosen after considering the question to be answered. The perfect model that fits all requirements does not exist. However, some of the current models allow us to analyze precise questions within the PD disease spectrum. At present, preclinical models and models to evaluate enteric signs, nigrostriatal neurodegeneration, the multiple hits hypothesis, and acute motor dysfunction, among others, are available. In the past, translational research has advanced using appropriate models to aid the development of deep-brain stimulations and L-DOPA treatments. The current trend in translational PD research is neuroprotection or reversion of neurodegeneration. This endeavor requires models that reproduce early pathogenic events such as those observed in transgenic models. Better clinical PD stratification and identification of triggering environmental factors will further increase the demand for targeted models. The need for distinct model platforms and for the development of targeted therapeutic interventions will grow with our knowledge on PD etiology and stratification.

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