Parkinson's Disease

Product Guide | Edition 1

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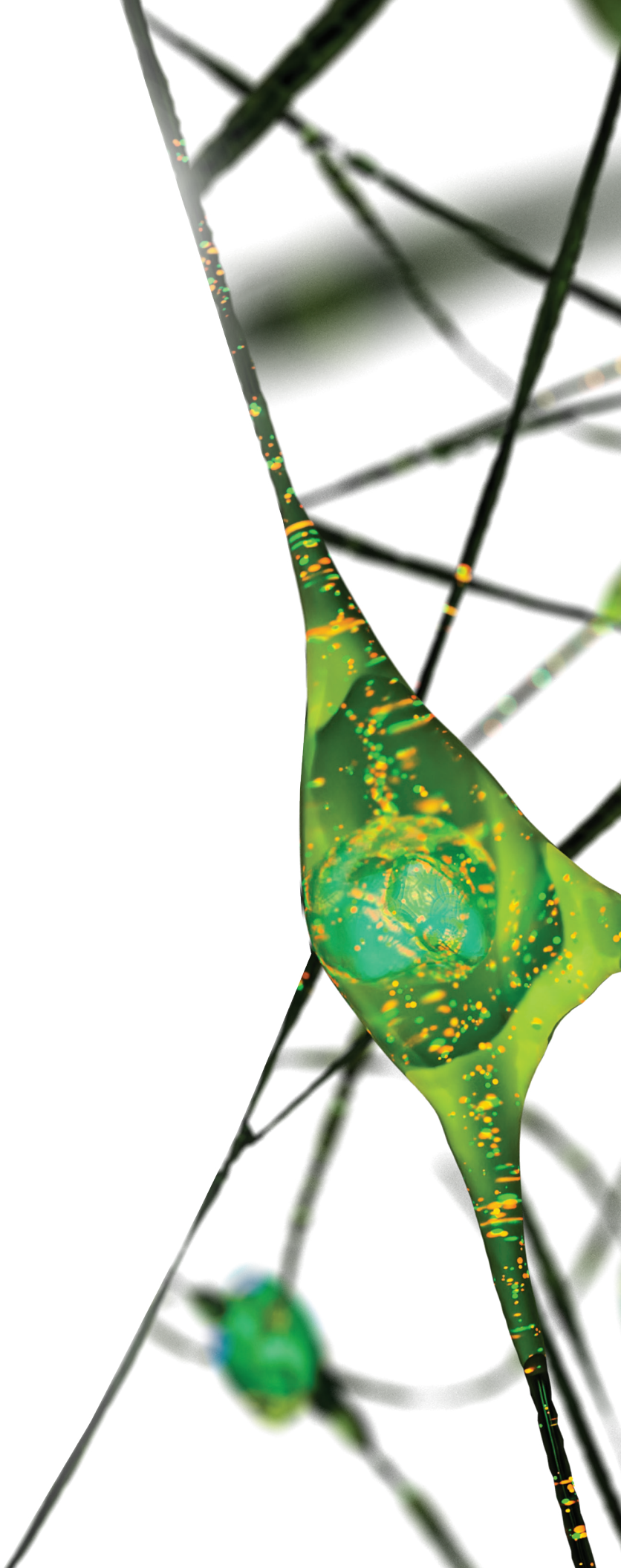
Parkinson's Disease

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that is principally characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). As the SNc is a component of the basal ganglia, this focal degeneration impairs motor learning, function and coordination; specifically, motor symptoms include tremor, bradykinesia, rigidity and postural instability. In addition, non-motor symptoms manifest in PD as early as 20 years before the first motor symptoms. This is known as the "prodromal phase" of the disease, and is driven by disturbances in neurotransmitter signaling that evolve into synaptic, and finally neuronal, loss.

The pathogenesis of PD has been proposed to be multifactorial with mitochondrial dysfunction, lysosomal dysregulation and α-synuclein aggregation and seeding being cited as major drivers behind the loss of dopaminergic neurons. Analysis of gene expression in PD patients has also revealed a genetic component of the disease, with mutations in a number of genes – including PRKN, PINK1, LRRK2, PARK7, SNCA and GBA all being linked to the development of PD. In rare cases of early-onset familial PD, mutations in a single gene are sufficient to drive the pathology, with LRRK2 risk variants being the most common cause of hereditary PD (hPD). Proteins encoded by these genes are under investigation to determine their influence on the pathogenesis of PD and their potential as a therapeutic target. Although the sporadic cases (sPD) have a stronger environmental risk factor influence, analysis of these PD-associated risk genes has provided significant advances in understanding the pathogenesis of the disease as a whole.



Etiology of Parkinson's Disease

The characteristic motor symptoms of PD occur as a result of the death of dopaminergic neurons in the SNc, a constituent of the basal ganglia. The basal ganglia are a collection of nuclei within the brain (Figure 1) that are integral to controlling motor function, learning and cognition. In the basal ganglia of healthy subjects, a network of inhibitory and excitatory neurons regulates signal transmission through the motor thalamus to the motor cortex. Dopaminergic neurons modulate this signaling network, both to facilitate movement (direct pathway) and to impede movement (indirect pathway). The correct balance of these antagonistic pathways enables coordinated motor control that is lost in PD.

Dopaminergic neurons in the SNc form one of many neuronal classes that coordinate the functional output of the basal ganglia. Others include the glutamatergic cortical projection neurons, serotonergic neurons of the dorsal raphe nucleus and GABAergic interneurons of the substantia nigra, all of which could be alternative targets for the treatment of PD.

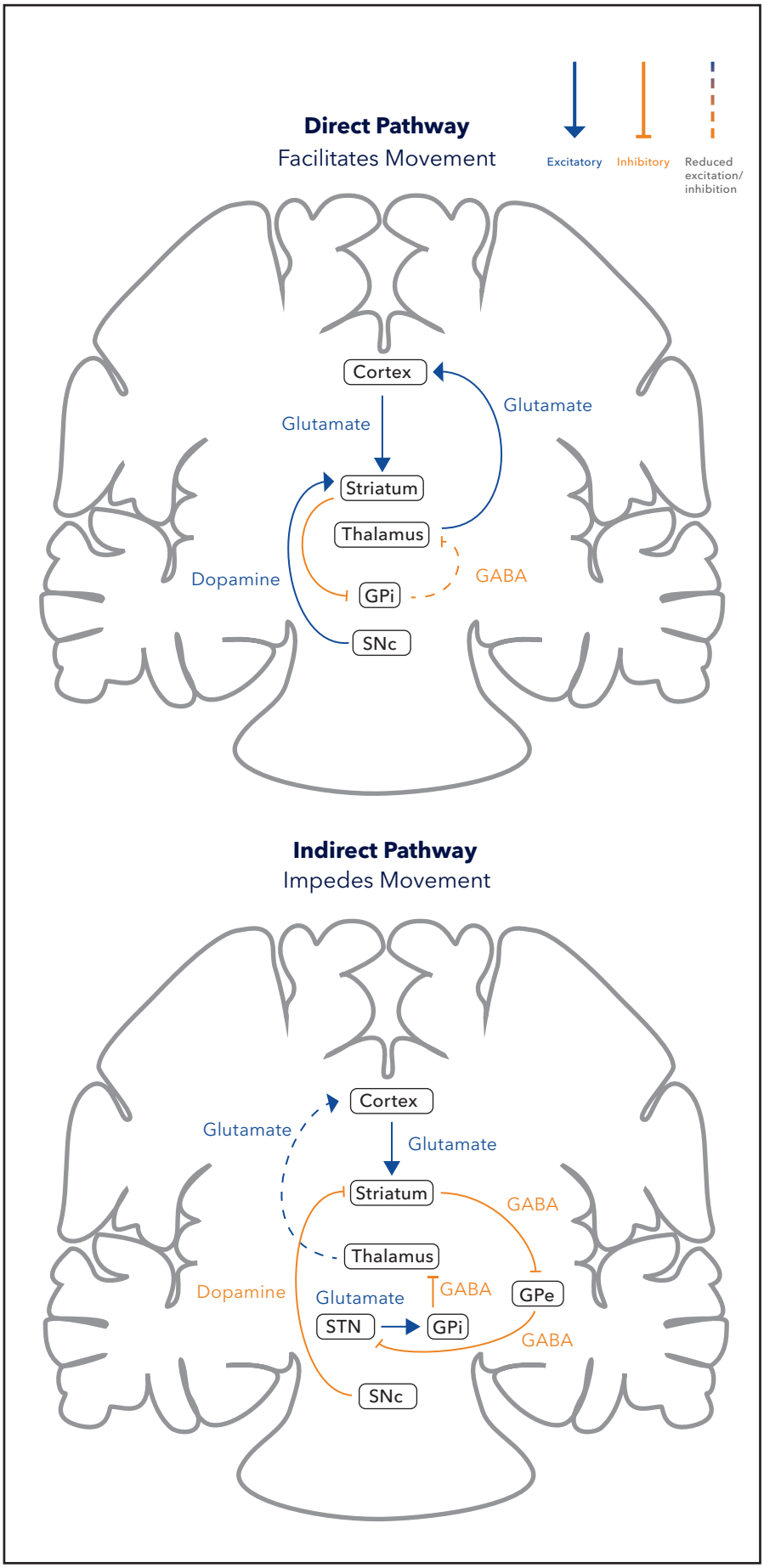


Figure 1: Direct and indirect pathways of the basal ganglia. The Direct Pathway corresponds to an overall increase in motor activity due to disinhibition of the thalamus. The Indirect Pathway, as seen in Parkinson's Disease, leads to the suppression of extemporaneous movement due to disinhibition of the subthalamus. (GPe - Globus pallidus externa; Gpi - Globus pallidus interna; STN - subthalamic nucleus; SNc - substantia nigra pars compacta).

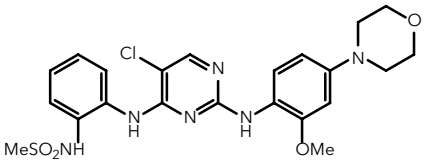
α-Synuclein

α-Synuclein is a neuronal protein that remains to be fully characterized and has been implicated in several pathways ranging from regulation of endocytosis/exocytosis, which modulates dopaminergic signaling, to mediation of the immune response. The gene encoding α-synuclein, SNCA, is a significant risk factor for sPD; the SNCA mutations detected in sPD are typically point mutations that are thought to promote α-synuclein oligomerization and fibrillogenesis, which lead to aggregate formation. These aggregates are "sticky" and can sequester other proteins to form Lewy Bodies. In sporadic, and some familial variants of PD, Lewy Bodies are a characteristic feature of the disease. Anti-α-synuclein antibodies are being tested in clinical trials with the aim of alleviating the overexpression and aggregation of α-synuclein and hopefully the disease burden.

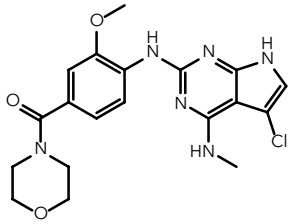
A key feature of mutant α-synuclein is that it is selectively and extensively phosphorylated at Ser129 and this has been shown to increase α-synuclein toxicity. Kinases implicated in α-synuclein Ser129 phosphorylation include Abelson tyrosine-protein kinase 1 (ABL1), casein kinase 1 (CK1), casein kinase 2 (CK2) and G-protein-coupled receptor kinase 2 (GRK2), amongst others. Targeting these kinases using inhibitors such as D 4476 (Cat. No. 2902), TBB (Cat. No. 2275) and GRK2i (Cat. No. 3594) block Ser129 phosphorylation and may therefore delay α-synuclein-mediated cytotoxicity .

An alternative strategy for targeting α-synuclein toxicity in PD is through the promotion of α-synuclein inclusion formation. This approach, though at first appearing paradoxical, is thought to exert a protective effect in PD by reducing the presence of toxic early aggregation intermediates such as oligomers. Using small molecules, such as β-glucocerebrosidase (GBA) activators, to promote the clearance of α-synuclein aggregates has shown promise in early stage clinical trials.

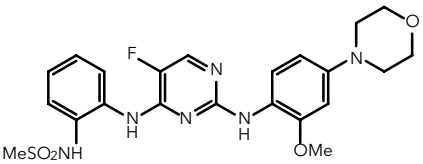
Box 1 LRRK2 inhibitors



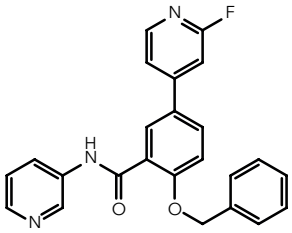
CZC 54252 (Cat. No. 4534)
Potent LRRK2 inhibitor; neuroprotective



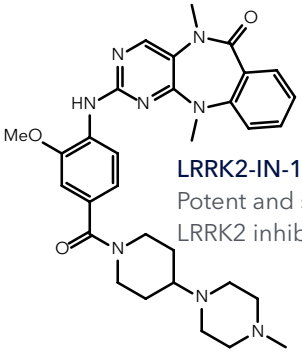
JH-II-127 (Cat. No. 6289)
Potent and selective LRRK2 inhibitor



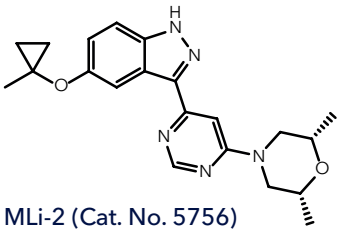
CZC 25146 (Cat. No. 6071)
Potent LRRK2 inhibitor



GSK2578215A (Cat. No. 4629)
Potent and selective LRRK2 inhibitor; brain penetrant



LRRK2-IN-1 (Cat. No. 4273)
Potent and selective LRRK2 inhibitor



MLi-2 (Cat. No. 5756)
Potent and selective LRRK2 inhibitor

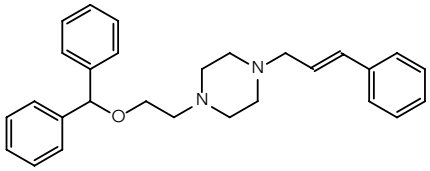
Lysosomal Dysregulation

A common feature seen across PD variants is the dysregulation of the lysosomal and autophagy pathways. LRRK2, a protein kinase which has been implicated in both sPD and hPD, regulates autophagosome and lysosome fusion. The most common LRRK2 mutation observed in PD is G2019S, a missense mutation that affects the kinase domain of LRRK2 and is thought to increase its autophosphorylation activity and to activate the neuronal death pathway. This gain-of-function mutation is associated with abnormal lysosomal morphology and impaired autophagosome formation, which promotes the formation of Lewy Bodies.

LRRK2 associates with α-synuclein and this interaction has been proposed to promote α-synuclein seeding. The potent and selective LRRK2 inhibitors Mli-2 (Cat. No. 5756), GSK2578215A (Cat. No. 4629), and LRRK2-IN-1 (Cat. No. 4273), may shed light on the function of LRRK2 and the extent of its involvement in PD (see Box 1 LRRK2 inhibitors), and LRRK2 inhibitors have reached clinical trials for PD. An alternative strategy, targeting specific degradation of LRRK2 can be explored with the development of LRRK2 PROTAC® molecules. PROTACs are bifunctional compounds that consist of binding moieties for the target (i.e. LRRK2) and E3 ubiquitin ligase, joined by a linker. This enables PROTACs to drive the selective ubiquitination of the target, leading to its subsequent degradation by the endogenous proteasome system. LRRK2 targeting PROTACs could therefore be a valuable tool in PD research.

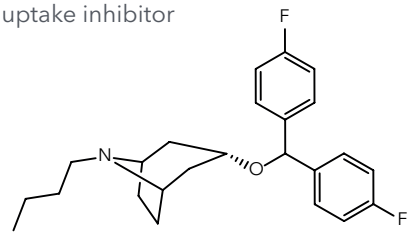
Glucocerebrosidase/β-glucosidase (encoded by the gene GBA) is a lysosomal enzyme responsible for degrading specific glycolipids. Loss-of-function mutations in GBA manifest as a lysosomal storage disorder, Gaucher disease, but can also be present in rare familial variants of PD. This particular variant of hPD typically progresses more aggressively and has a greater non-motor symptom clinical profile compared to sPD. Further research using GBA activators and inhibitors (e.g. Conduritol B epoxide, Cat. No. 7056) could provide useful insight into the lysosomal dysfunction seen in PD.

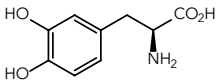
Box 2 Dopamine and dopamine transporters



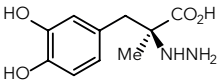
GBR 12783 (Cat. No. 0513)
Potent and selective dopamine uptake inhibitor

JHW 007 (Cat. No. 4351)
High affinity dopamine uptake inhibitor





(*S*)-(-)-Carbidopa (Cat. No. 0455)
L-amino acid decarboxylase inhibitor



L-DOPA (Cat. No. 3788)
Dopamine precursor

Mitochondrial Dysfunction

It is thought that the selective death of dopaminergic neurons in PD is linked to an increased vulnerability of these neurons to external cell death-inducing stimuli. This is exemplified in the response of nigrostriatal dopaminergic neurons to the mitochondrial complex I inhibitor Rotenone (Cat. No. 3616); although rotenone is distributed uniformly throughout the brain following administration, the development of cytoplasmic inclusions and subsequent neuronal death selectively affects nigrostriatal dopaminergic neurons. By using a mouse conditional knockout of the mitochondrial complex I catalytic core in dopaminergic neurons, it has been shown that this is sufficient to trigger motor learning and function deficits. The experimental tool CGP 3466B (TCH 346, Cat. No. 2966), a GAPDH inhibitor that blocks mitochondrial complex I-mediated hydrogen peroxide release, prevents dopaminergic neuron loss in animal models of PD, demonstrating the importance of complex I as a target for PD research.

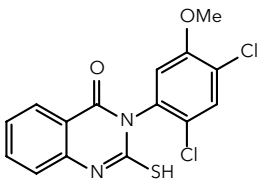
The environmental toxin 1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP) also inhibits complex I activity and can be used as a tool to induce PD-like symptoms in experimental models of the disease. MPTP itself is not toxic, but when metabolized *in vivo* by monoamine oxidase B (MAO-B), it forms 1-methyl-4-phenyl-pyridium (MPP^+). This toxic metabolite is concentrated in the mitochondria by the dopamine transporter, which leads to complex I inhibition, depolarization of the mitochondrial membrane and opening of the mitochondrial permeability transition pore (mPTP). MAO-B inhibitors, Rasagiline (Cat. No. 4308) and Lazabemide (Cat. No. 2460) block the metabolism of MPTP, preventing the formation of toxic MPP^+. Other experimental tools that can be used to study the effects of MPTP include the dopamine transporter inhibitors GBR 12909 (Cat. No. 0421) and JHW 007 (Cat. No. 4351), (see Box 2 Dopamine and dopamine transporters).

Complex I dysfunction in the absence of exposure to complex I inhibitors has been observed in post-mortem studies of PD brains, suggesting that its downstream effects may elucidate other targets for PD research. In particular, targeting mediators of cell death which are activated following loss of complex I activity, such as Bax, AIF and cytochrome c, may uncover novel strategies for neuroprotection. Inhibitors of Bax, such as Bax channel blocker (Cat. No. 2160), and iMAC2 (Cat. No. 3794) may be useful for studying these mechanisms.

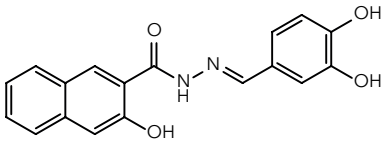
Dopaminergic neurons are particularly vulnerable to the effects of mitochondrial complex I inhibition because, unlike the majority of other neurons, they express $Ca_V1.3$-containing L-type calcium channels. These $Ca_V1.3$-containing channels exhibit an increased ATP consumption and calcium flux due to their role in pacemaking, properties which render them more susceptible to oxidative stress and cell death. The effect of this unusual property was first demonstrated in a Danish study of hypertensive patients: administration of brain-penetrant L-type calcium channel blockers such as Verapamil (Cat. No. 0654), Diltiazem (Cat. No. 0685) and Isradipine (Cat. No. 2004) was associated with a significant decrease in the risk of developing PD. This effect has since been attributed to $Ca_V1.3$ channels, which therefore represent an attractive therapeutic target for PD. More recently, T- and R-type calcium channels have also been implicated in PD pathology with a selective T-type calcium channel blocker currently in clinical trials for essential tremor.

Other mitochondrial proteins postulated to be involved in PD include PINK1, PARK7, and parkin. These proteins are either located within the mitochondria or, in the case of parkin, are directly recruited by mitochondrial proteins. They are vital for the healthy function of the mitochondria, regulating processes including: biogenesis, mitophagy and mitochondrial trafficking. Rare loss-of-function mutations in the genes encoding these proteins are linked to specific forms of familial early-onset PD, as well as single-nucleotide polymorphisms

Box 3 Dynamin inhibitors



Dynasore (Cat. No. 2897)
Inhibitor of dynamin 1, dynamin 2 and mitochondrial dynamin



Mdivi 1 (Cat. No. 3982)
Selective dynamin inhibitor; attenuates mitochondrial division and apoptosis

Tyr-Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Arg-Gly-Gly-Asp-Leu-Leu-Pro-Arg-Gly-Ser-NH_2

P110 (Cat. No. 6897)
Dynamin-related protein 1 inhibitor

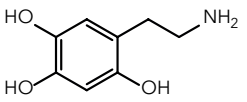
associated with the risk of developing sporadic PD. Restoring mitochondrial homeostasis could be a novel therapeutic strategy in PD. Research tools such as: Staurosporine (Cat. No. 1285), an activator of PINK1–parkin pathway dependent mitophagy, Mdivi 1 (Cat. No. 3982) a dynamin inhibitor, and P110 (Cat. No. 6897) and Drpitor1a (coming soon, Cat. No. 7674), both inhibitors of dynamin-related protein 1, may prove useful (see Box 3 Dynamin inhibitors). USP30 inhibitors can also compensate for the loss of function of PRKN, for example ±-MF 094 (Cat. No. 6718).

Depletion of Dopaminergic Signaling

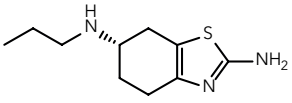
The death of dopaminergic neurons has severe effects on motor function due to the involvement of dopamine in modulating motor activity (Figure 1). In order to address the decreased dopamine availability in PD, treatment has classically involved administering L-DOPA (Cat. No. 3788, see Box 2), a precursor to dopamine that (unlike dopamine) can cross the blood-brain barrier. However, dosing regimens frequently result in fluctuations in L-DOPA levels, leading to periods of dyskinesia and psychosis. L-DOPA-induced dyskinesia remains a significant problem for PD patients despite L-DOPA being accepted as a 'gold standard' for the treatment of PD. Subsequent preclinical and clinical studies have demonstrated that co-administration with the catechol-O-methyltransferase (COMT) inhibitor opicapone helps maintain a more consistent delivery of L-DOPA, and is now the recommended course of treatment in PD. The availability of L-DOPA is negatively affected by the activity of COMT and DOPA decarboxylase (DDC) and therefore co-administering inhibitors of these enzymes with L-DOPA increases L-DOPA's efficacy. COMT inhibitors prevent the conversion of the therapeutically active L-DOPA into 3-O-methyldopa, a metabolite with no therapeutic effect that competes with L-DOPA for transport into the brain. DDC inhibitors such as (*S*)-(-)- Carbidopa (Cat. No. 0455) prevent metabolism of L-DOPA in the periphery, thereby increasing central penetration of L-DOPA.

Further strategies to compensate for the loss of dopaminergic signaling in PD include the use of post-synaptic dopamine D_2/D_3 receptor agonists such as Pramipexole (Cat. No. 4174), Rotigotine (Cat. No. 3896), Cabergoline (Cat. No. 2664), Bromocriptine (Cat. No. 0427) and Ropinirole (Cat. No. 3680) (see Box 4 Dopamine receptor agonists). These mimic the effects of the depleted dopaminergic neurons within the basal ganglia and improve motor function. However, current FDA approved dopamine receptor agonists also exhibit undesirable side-effects including nausea, dyskinesias and hallucinations and so newer, non-dopaminergic targets are now a focus of research.

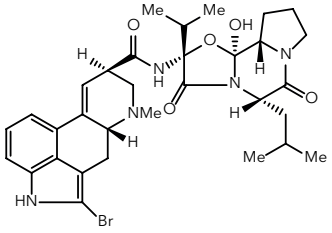
Box 4 Dopamine receptor agonists



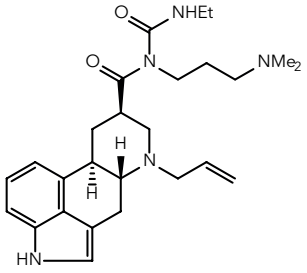
6-Hydroxydopamine hydrobromide (Cat. No. 2547)
Selective catecholaminergic neurotoxin



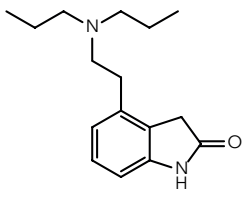
Pramipexole (Cat. No. 4174)
Selective D_3 agonist



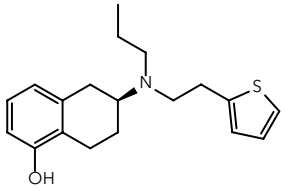
Bromocriptine (Cat. No. 0427)
Selective D_2-like dopamine receptor agonist



Cabergoline (Cat. No. 2664)
D_2-like dopamine receptor agonist



Ropinirole (Cat. No. 3680)
Selective D_2-like receptor agonist



Rotigotine (Cat. No. 3896)
Dopamine D_2 and D_3 receptor agonist

One such non-dopaminergic target under investigation is 5-HT receptors. Often implicated in the pathogenesis and treatment of mood disorders, 5-HT_{1A} receptors have also been linked to PD due to the involvement of serotonergic neurons in controlling motor function, and the observation that they are also depleted in PD patients. Experimental tools for 5-HT receptors, in particular agonists such as 8-hydroxy-DPAT (Cat. No. 0529) and Tandospirone (Cat. No. 2854) may enable researchers to determine the influence of 5-HT on PD. Interestingly a 5-HT_{2A} inverse agonist is being investigated in clinical trials for treatment of PD-associated psychosis.

Stem Cells

Neurons derived from stem cells have been used for drug screening and the pathogenesis of PD may be modeled using stem cell-derived neurons.

PD has been a focus of significant stem cell research, due to the fact that a specific type of neuron and discrete brain region are involved. This profile has enabled researchers to develop and optimize *in vitro* neuronal differentiation paradigms that efficiently generate midbrain dopaminergic-like neurons from human embryonic stem cells (hESC). Work has been done to show that precise timing and dosing of specific small molecules, including SB 431542 (Cat. No. 1614), LDN 193189 (Cat. No. 6053), and CHIR 99021 (Cat. No. 4423), can be used to recapitulate endogenous developmental conditions to generate midbrain dopaminergic neuron-like cultures from hESC. Moreover, the neurodegeneration profile of PD favors the use of regenerative medicine strategies. With established protocols for generating an unlimited source of hESC-derived dopaminergic progenitors, the clinical reality of regenerative medicine has drawn closer and phase I clinical trials are in progress for the treatment of PD with transplanted patient stem cell-derived neurons.

Future Directions

The identification of multiple gene mutations associated with PD has provided a new set of molecular targets for the focus of future PD research, whilst further genetic analysis may uncover additional molecular targets involved in PD. The availability of potent and selective tool compounds, such as LRRK2 inhibitors, GBA activators and calcium channel blockers, will enable researchers to elucidate the contribution of these individual proteins to the pathogenesis of PD and may lead to an efficacious therapy that not only alleviates both the motor and non-motor symptoms, but achieves this goal without causing side-effects.

List of Acronyms

Acronym	Definition
ABL1	Abelson tyrosine-protein kinase 1
CK1	Casein kinase 1
CK2	Casein kinase 2
COMT	Catechol-O-methyltransferase
DDC	DOPA decarboxylase
FDA	Food and Drug Administration
GBA	β-glucocerebrosidase
GRK2	G-protein-coupled receptor kinase 2
hESC	Human embryonic stem cells
hPD	Hereditary Parkinson's disease
mPTP	Mitochondrial permeability transition pore
MPTP	1-methyl-4-phenyl-1,2,3,6 tetrahydropyridine
PD	Parkinson's Disease
sPD	Sporadic Parkinson's disease
SNc	Substantia nigra pars compacta
SNCA	The gene that encodes α-synuclein

Products

	Cat. No.	Product Name	Primary Action
5-HT Receptors			
Agonists	0529	8-Hydroxy-DPAT	Selective 5-HT_{1A} agonist
	2854	Tandospirone	Selective 5-HT_{1A} partial agonist
14.3.3 Proteins			
Inhibitors	2144	R18	Inhibitor of 14.3.3 proteins
Adenosine Receptors			
Agonists	1063	CGS 21680	Potent A_{2A} adenosine receptor agonist
Antagonists	1036	ZM 241385	Potent and highly selective A_{2A} antagonist
Adrenergic β_2 Receptors			
Agonists	0634	Salbutamol	β2-adrenoceptor agonist
Autophagy			
Activators	1292	Rapamycin	mTOR inhibitor; induces autophagy
	4297	SMER 28	Positive regulator of autophagy
	7474	EN6	Activator of autophagy; inactivates mTORC1 signaling
Bcl-2 Family			
Inhibitors	2160	Bax channel blocker	Allosteric inhibitor of Bax channel activation
	3794	iMAC2	Suppressor of mitochondrial apoptosis; Bax inhibitor
Calcium Channels			
Blockers	0654	Verapamil	Ca_V1.x blocker
	0685	Diltiazem	Ca_V1.x blocker
	2004	Isradipine	Potent and selective Ca_V1.x blocker
Casein Kinase 1			
Inhibitors	2902	D4476	Selective CK1 inhibitor; also inhibits TGF-βRI
Casein Kinase 2			
Inhibitors	2275	TBB	Selective cell-permeable CK2 inhibitor
Decarboxylases			
Inhibitors	0455	(*S*)-(-)-Carbidopa	Aromatic L-amino acid decarboxylase inhibitor
Dehydrogenases			
Inhibitors	2966	CGP 3466B	GAPDH inhibitor; neuroprotective

Deubiquitinating Enzymes			
Inhibitors	6718	±-MF 904	Selective USP30 inhibitor
Dopamine			
Other	3788	L-DOPA	Dopamine precursor
Dopamine Receptors			
Agonists	3548	Dopamine	Endogenous agonist at dopamine D_{1-5} receptors
	4174	Pramipexole	Selective D_3 agonist
	3896	Rotigotine	D_2 and D_3 agonist
	2664	Cabergoline	selective D_2-like dopamine receptor agonist
	0427	Bromocriptine	selective D_2-like dopamine receptor agonist
	3680	Ropinirole	selective D_2-like dopamine receptor agonist
Other	2547	6-Hydroxydopamine	Selective catecholaminergic neurotoxin
Dopamine Transporters			
Inhibitors	0421	GBR 12909	Potent, competitive inhibitor of dopamine uptake
	4351	JHW 007	High affinity dopamine uptake inhibitor
	0513	GBR 12783	Potent and selective DA uptake inhibitor
Ferroptosis			
Inhibitors	5180	Ferrostatin 1	Selective inhibitor of erastin induced ferroptosis
	6118	1S,3R-RSL3	Ferroptosis inducer; inhibits glutathione peroxidase (GPX4)
$GABA_A$ Receptors			
Agonists	0289	Muscimol	Potent $GABA_A$ agonist; also $GABA_A$-ρ partial agonist
Antagonists	1128	Picrotoxin	$GABA_A$ antagonist
$GABA_B$ Receptors			
Agonists	4709	RuBi GABA trimethylphosphine	Caged GABA; inhibits neural activity
Antagonists	1245	CGP 35348	Selective $GABA_B$ antagonist; brain penetrant
Glutamate (Ionotropic) Receptors			
Antagonists	0112	γDGG	Broad spectrum glutamatergic antagonist
	3694	Kynurenic acid sodium salt	Broad spectrum EAA antagonist
Glutamate (Metabotropic) Receptors			
Agonists	3695	CHPG Sodium salt	Selective $mGlu_5$ agonist
	3246	LY 354740	Potent and highly selective group II mGlu agonist
	0103	L-AP4	Selective group III mGlu agonist
Antagonists	1212	MPEP	Potent $mGlu_5$ antagonist; positive allosteric modulator of mGlu4 receptors
	1237	LY 367385	Selective $mGlu_{1a}$ antagonist

Glycosylases			
Inhibitors	7056	Conduritol B epoxide	Irreversible glucocerebrosidase (β-glucosidase) inhibitor
GTPases, Dynamin			
Inhibitors	3982	Mdivi 1	Selective dynamin inhibitor; attenuates mitochondrial division and apoptosis
	6897	P110	Dynamin-related protein 1 (Drp1) inhibitor
	2897	Dynasore	Non-competitive dynamin inhibitor
GTPases, Heterotrimeric G-protein			
Inhibitors	3594	GRK2i	GRK2 inhibitory polypeptide; Gβ/γ antagonist
Heat Shock Proteins			
Hsp70 inhibitors	3803	VER 155008	Hsp70 inhibitor
Hsp90 inhibitors	4701	EC 144	High affinity, potent and selective Hsp90 inhibitor
	3387	Gedunin	Hsp90 inhibitor; anticancer and antimalarial
	1515	17-AAG	Selective Hsp90 inhibitor
LRRK2			
Inhibitors	6071	CZC 25146	Potent LRRK2 inhibitor
	4534	CZC 54252	Potent LRRK2 inhibitor; neuroprotective
	4629	GSK2578215A	Potent, selective LRRK2 inhibitor; brain penetrant
	6289	JH-II-127	Potent and selective LRRK2 inhibitor
	4273	LRRK2-IN-1	Potent and selective LRRK2 inhibitor
	5756	MLi-2	Potent and selective LRRK2 inhibitor
Monoamine Oxidases			
Inhibitors	4308	Rasagiline	Selective and irreversible MAO-B inhibitor
	2460	Lazabemide	Selective MAO-B inhibitor
	6067	M 30	Potent and non-selective MAO inhibitor
Neural Stem Cells			
Other	1614	SB 431542	Potent, selective inhibitor of TGF-βRI, ALK4 and ALK7
	6053	LDN 193189	Potent, selective ALK2 and ALK3 and BMP4 signaling inhibitor; promotes neural induction of hPSCs
	4423	CHIR 99021	Highly selective GSK-3 inhibitor; acts as Wnt activator
	4366	SAG	Potent Smoothened receptor agonist
Oxidative Phosphorylation			
Inhibitors	3616	Rotenone	Inhibits complex I of the mitochondrial electron transport chain
	0453	FCCP	Potent oxidative phosphorylation uncoupler
	6980	BAY 87-2243	Mitochondrial complex I inhibitor

Phosphodiesterases			
Inhibitors	0905	Rolipram	PDE4 inhibitor
	1694	Ibudilast	Non-selective PDE inhibitor
	3784	Sildenafil	Potent PDE5 inhibitor
Poly(ADP-ribose) Polymerases			
Inhibitors	6461	PARPi-FL	Potent fluorescent PARP inhibitor; cell permeable
	3255	PJ 34	Potent PARP inhibitor
Prion Proteins			
Other	6861	Anle138b	Inhibits prion protein and α-synuclein aggregate formation
Protein Kinases			
Activators	1285	Staurosporine	Non-selective protein kinase inhibitor
σ Receptors			
Antagonists	3133	NE 100	Selective σ1 antagonist
Trk (neurotrophin) Receptors			
Agonists	2837	BDNF (human)	Activates TrkB and p75 receptors
	4607	LM 22A4	Potent TrkB agonist
	6037	LM22B 10	TrkB and TrkC agonist
Antagonists	4781	ANA 12	TrkB receptor antagonist
Other	2272	Ro 08-2750	Inhibits NGF binding to p75NTR and TrkA
	5046	LM11A 31	Nonpeptide $p75^{NTR}$ ligand; neuroprotective
Ubiquitin E3 Ligases			
Other	5131	NAB 2	Protects against α-synuclein toxicity; promotes Rsp5/ Nedd4-dependent endosomal transport
Vesicular Monoamine Transporters			
Inhibitors	2175	Tetrabenazine	Potent inhibitor of vesicular monoamine transport
Other	5043	FFN 206	Fluorescent VMAT2 substrate

Further Reading

Please refer to the list of recommended papers for more information.

Alam *et al* (2022) Alpha synuclein, the culprit in Parkinson disease, is required for normal immune function. *Cell Rep*. **38** 110090

Balestrino and Schapira (2020) Parkinson disease. *Eur. J.* Neurol. **27** 27

Buratti (2021) Targeting TDP-43 proteinopathy with drugs and drug-like small molecules. Br. *J. Pharmacol*. **178** 1298

Dawson and Dawson (2019) Promising disease-modifying therapies for Parkinson's disease. *Sci. Transl. Med.* **11** eaba1659

Doric and Nakamura (2021) Principles of Parkinson's disease disputed by model. *Nature* **599** 558

Earley *et al* (2021) Identification of ASCL1 as a determinant for human iPSC-derived dopaminergic neurons. *Sci. Rep*. **11** 22257

El Marabti and Abdel-Wahab (2021) Therapeutic Modulation of RNA Splicing in Malignant and Non-Malignant Disease. *Trends Mol. Med*. **27** 643

Fletcher *et al* (2021) Drug repurposing strategies of relevance for Parkinson's disease. *Pharmacol. Res. Perspect*. **9** e00841

Giusto *et al* (2021) Pathways to Parkinson's disease: a spotlight on 14-3-3 proteins. *NPJ Parkinsons Dis*. **7** s41531-021-00230-6

González-Rodríguez *et al* (2021) Disruption of mitochondrial complex I induces progressive parkinsonism. *Nature* **599** 650

Haque *et al* (2022) Targeting α-synuclein aggregation and its role in mitochondrial dysfunction in Parkinson's disease. *Br. J. Pharmacol*. **179** 23

Harris *et al* (2020) Emerging regenerative medicine and tissue engineering strategies for Parkinson's disease. *NPJ Parkinsons Dis*. **6** s41531-019-0105-5

Kim *et al* (2021) Biphasic Activation of WNT Signaling Facilitates the Derivation of Midbrain Dopamine Neurons from hESCs for Translational Use. *Cell Stem Cell* **28** 343

Krahn *et al* (2020) Defining the Neural Kinome: Strategies and Opportunities for Small Molecule Drug Discovery to Target Neurodegenerative Diseases. *ACS Chem. Neurosci.* 11 1871

Lambourne and Mehellou (2018) Chemical Strategies for Activating PINK1, a Protein Kinase Mutated in Parkinson's Disease. *Chembiochem.* **19** 2433

Lengyel-Zhand *et al* (2022) PARkinson's: From cellular mechanisms to potential therapeutics. *Pharmacol. Ther.* **230** 107968

Madureira *et al* (2020) LRRK2: Autophagy and Lysosomal Activity. Front. *Neurosci.* **14** 498

Mirzaei *et al* (2021) Biomaterial Strategies for Restorative Therapies in Parkinson's Disease. ACS Chem. *Neurosci.* **12** 4224

Nalls *et al* (2019) Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol.* **18** 1091

Nandakumar *et al* (2021) Interventional Strategies for Parkinson Disease: Can Neural Precursor Cells Forge a Path Ahead? ACS Chem. *Neurosci*. **12** 3785

Oliveira *et al* (2021) Alpha-synuclein research: defining strategic moves in the battle against Parkinson's disease. *NPJ Parkinsons Dis*. **7** s41531-021-00203-9

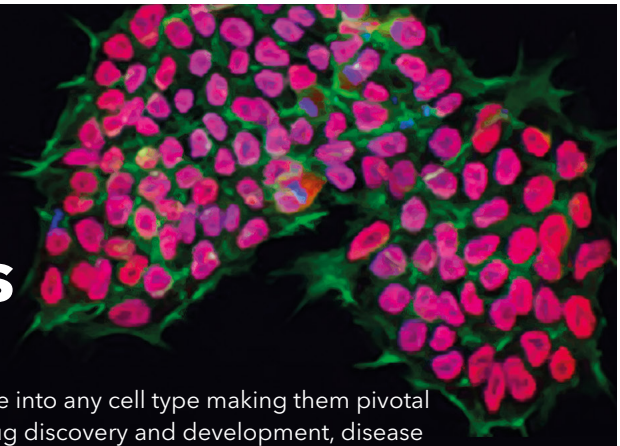
Piao et al (2021) Preclinical Efficacy and Safety of a Human Embryonic Stem Cell-Derived Midbrain Dopamine Progenitor Product, MSK-DA01. *Cell Stem Cell* **28** 217

Pujols *et al* (2020) Chemical Chaperones as Novel Drugs for Parkinson's Disease. *Trends Mol. Med.* **26** 408

Ravina *et al* (2012) Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson's Disease. *Mov. Disord.* **27** 1392

Senkevich *et al* (2022) New therapeutic approaches to Parkinson's disease targeting GBA, LRRK2 and Parkin. *Neuropharmacology* **202** 108822

Consistent Reagents for Consistent Cultures



Pluripotent stem cells (PSCs) have the potential to differentiate into any cell type making them pivotal tools for a variety of applications including basic research, drug discovery and development, disease modeling, toxicology testing, cell therapy and personalized medicine. The reagents and protocols needed to culture, differentiate and characterize PSC-derived cells vary by cell type. At Bio-Techne we are proud to offer a portfolio of research tools that you can trust for your PSC cultures.

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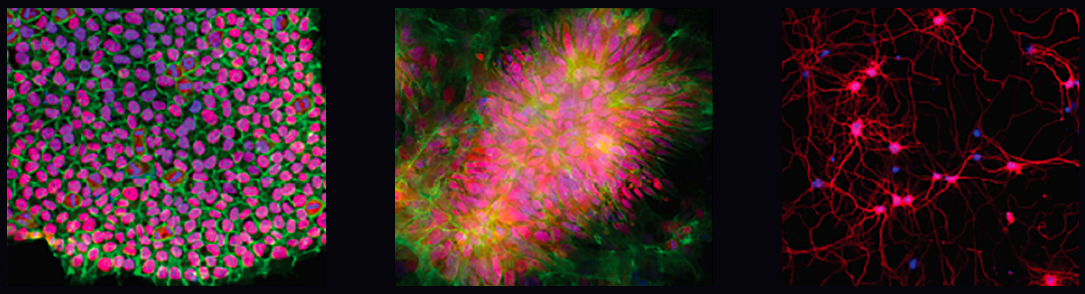

Human induced pluripotent stem cells (HiPSCs) maintained in ExCellerate™ iPSC Expansion Medium (Catalog # CCM036) differentiate into neurons using the StemXVivo™ Neural Progenitor Differentiation Kit (Catalog # SC035) or using research-grade or GMP-grade proteins, small molecules, and supplements: GMP SB 431542 (Catalog # 1614 or TB1614-GMP), Recombinant Human Noggin (Catalog # 6057-NG or 6057-GMP), Recombinant Human FGF basic (Catalog # 233-FB or 233-GMP), N-2 MAX Media Supplement (Catalog # AR009 or AR016), and N21-MAX Media Supplement (Catalog # AR008). Cells were stained with antibodies to Oct-3/4, E-Cadherin, Pax6, Actin, and Tuj plus DAPI.

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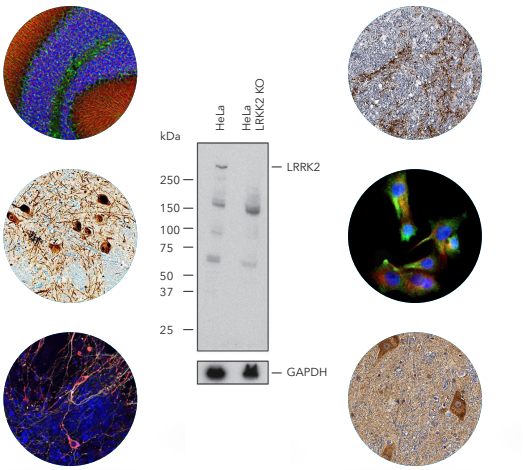

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