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Neurodegeneration

Product Guide | Edition 2 | USD

Passion Flower
Passiflora caerulea
A source of Harmane

Contents by Research Area:

- Neurodegeneration
- Alzheimer's Disease
- Parkinson's Disease
- Huntington's Disease

Neurodegeneration Research

Contents

Introduction

Neurodegenerative diseases are highly prevalent disorders for which the greatest risk factor is increasing age. The pathogenesis of these disorders is yet to be fully understood, and current research efforts are focused on elucidating the cellular and molecular mechanisms responsible, with the hope that drugs that prevent or reverse disease progression will be discovered. Three of the major neurodegenerative diseases are Alzheimer's disease, Parkinson's disease and Huntington's disease, which are discussed in this product guide. Research into these disorders has so far yielded few drugs that have proven effective in clinical trials, and many current therapies are targeted at attenuating disease symptoms, rather than disease progression.

Due to the prevalence of neurodegenerative diseases, they constitute a significant human, societal and economic burden. The global financial cost far outweighs other disorders such as stroke, musculoskeletal disease, heart disease or cancer. Given the aging population, the incidence of neurodegenerative disorders is predicted to rise; early diagnosis and effective treatment is of paramount importance, and these rely on a greater understanding of the mechanisms that underlie each disorder.

Included in this guide are key compounds used in the study of Alzheimer's, Parkinson's and Huntington's disease, as well as illustrative schematics of the molecular mechanisms thought to contribute to each disease. The use of small molecule inhibitors and antagonists to facilitate such research has helped delineate the pathways involved in these diseases, as well as providing a solid foundation for the development of future targeted therapeutics. Tocris provides an innovative range of high performance life science reagents for use in neurodegeneration research, equipping researchers with selective pharmacological tools for studying these disease pathways. A full product listing can be found on pages 24-33.

Key Neurodegeneration Research Products

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Neurodegeneration

Neurodegeneration is the progressive death of neurons in the brain that leads to a loss of structure and function. Alzheimer's, Parkinson's and Huntington's disease are the three major disorders that develop as a result of neurodegeneration, and will be discussed in this guide. Each disorder has characteristic symptoms in the early stages of the disease, such as the cognitive decline associated with the onset of Alzheimer's; a loss of motor control, which is often an early indicator of Parkinson's disease; or behavioral changes symptomatic of Huntington's disease. As we age, our susceptibility to these diseases increase, and it is thought that this may be due to an increased vulnerability of particular neuronal populations within defined areas of the brain. It is worth noting that approximately 10% of neurons die as a consequence of 'healthy', non-pathological aging; indeed, protein aggregates synonymous with Alzheimer's disease have also been observed in asymptomatic patients.

As a population ages, the prevalence of neurodegeneration is likely to increase. Effective treatments to prevent progression of neurodegenerative disorders are notably absent with no strong candidates currently on the horizon. Alzheimer's disease, the most prevalent neurodegenerative disease worldwide, was estimated to affect 35.6 million people in the world in 2010 and it is thought that the numbers of those affected will almost double every 20 years*, in line with an aging population.

The mechanisms that lead to neuronal cell death in neurodegenerative diseases are not well understood. However, it is believed that neurodegenerative diseases have common cellular and molecular mechanisms. Dysregulation of protein synthesis, degradation and transport, alongside hallmark features such as protein misfolding, accumulation into aggregates as well as inclusion body formation, are characteristic of all three diseases that will be covered in this guide. A recently identified mechanism applicable to all neurodegenerative diseases describes how cell death may occur: a build-up of misfolded proteins in the brain over-activates a natural defensive mechanism – the unfolded protein response – which switches off the production of new proteins. This effectively starves the neuron of the proteins it needs for normal function and triggers cell

Table 1 | Characteristics of Alzheimer's disease, Parkinson's disease and Huntington's disease

	Alzheimer's Disease	Parkinson's Disease	Huntington's Disease
Histopathological hallmarks	Loss of neurons in temporal/frontal lobes, neocortex and hippocampus Neurofibrillary tangles Amyloid plaques Hyperphosphorylated tau protein	Loss of dopaminergic neurons in the substantia nigra Lewy bodies	Loss of medium spiny neurons in the striatum N-terminal toxic fragments of mutant huntingtin protein Intranuclear inclusion bodies
Worldwide prevalence	200 per 100,000	160 per 100,000	4-10 per 100,000
Average age of onset	65 years	62 years	40 years (N.B. wide variation)
Dyskinesia	Absent	Present	Present
Major brain areas affected	Cortex, striatum and thalamus	Substantia nigra, basal ganglia	Striatum
Oxidative stress?	Yes	Yes	Yes
Protein misfolding?	Yes	Yes	Yes
Disease-associated proteins	A□ peptide Tau	α-Synuclein	Mutant huntingtin
Established experimental models	APP mutant mouse 3xTg-AD mouse (Tg2576)	6-OHDA lesions MPTP treatment	R6/2 transgenic fragment model Quinolinic acid lesions YAC128 transgenic full-length model
Number of current clinical trials†	533	494	159
Associated genes	*APP* *PS1* *PS2* *ApoE4*	*PINK1* *DJ-1* *Parkin* *SNCA* *LRRK2* *ATP13A2*	*IT15*
Causal factors	Unknown	Unknown	PolyQ expansion resulting in generation of mutant protein
Current therapeutics	Memantine Cholinesterase inhibitors	L-DOPA	Tetrabenazine Antipsychotics

*Statistics obtained from www.alz.co.uk/research/statistics on October 17, 2013
†Data obtained from www.clinicaltrials.gov on September 04, 2015

death. Researchers are targeting this mechanism by trying to block the 'off' switch in studies that may be a possible turning point for the treatment of all neurodegenerative diseases.

Neurons have machinery that helps defend against the build-up of misfolded and aggregated proteins. If chaperone proteins fail to induce proper folding, abnormal proteins can be targeted for degradation by attachment of polyubiquitin and targeting to the proteasome for degradation. Similarly, the autophagy/lysosomal pathways are known to arbitrate between neuronal survival and death. When these processes are compromised, however, they can play critical roles in the pathogenesis of neurodegenerative diseases.

A genetic component is evident in many neurodegenerative diseases. Huntington's disease is a well-characterized polyglutamine disorder, in which a repeat of the CAG sequence – which encodes the amino acid glutamine – generates a polyglutamine tract. These extra glutamine residues induce irregular protein folding and alter protein function, which is toxic to the cell. Alzheimer's and Parkinson's disease also have a genetic component, with genetic analysis identifying numerous genes associated with each disorder, including *ApoE4*, *PINK1* and *LRRK2* (Table 1). A key example of the genetic element of Alzheimer's is evident in people with Down Syndrome who have a third copy of chromosome 21. The gene that is involved in production of the toxic amyloid β plaques in Alzheimer's disease is also located on chromosome 21. People with Down Syndrome who have this extra gene copy almost universally exhibit Alzheimer's disease by 40 years of age.

Oxidative stress is another key characteristic that underlies neurodegenerative diseases. Evidence of reactive oxygen species that are toxic to cells have been described in affected brain regions of Alzheimer's and Parkinson's disease patients. Oxidative stress not only damages cells but can trigger programmed cell death, leading to neurodegeneration. However it is unknown whether the widespread neuronal cell death seen in neurodegenerative diseases is caused by oxidative stress, or is coincident with it; therefore, strategies to therapeutically inhibit oxidative stress may help decrease cell death.

Although neurodegenerative diseases exhibit similarities in the cellular events which occur during the course of disease, there are substantive differences between each disorder which necessitate tailored therapeutic strategies. An example of where this is evident is in the effects of L-DOPA – this drug alleviates motor symptoms in Parkinson's disease yet it exacerbates motor dysfunction in Huntington's disease, despite the two diseases sharing a common cause of protein misfolding.

Disease-specific mechanisms are outlined and discussed in more detail in the following sections: Alzheimer's disease (p5), Parkinson's disease (p12) and Huntington's disease (p17). Further work into such mechanisms may elucidate therapies to successfully target neurodegenerative diseases.

Alzheimer's Disease

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a loss of cognitive function. Neurodegeneration in the neocortex and hippocampus – regions of the brain involved in higher functions such as sensory perception, language and memory – lead to symptoms often initially associated with dementia. Indeed, AD is the most common neurodegenerative disease, accounting for 60-80% of all dementias. AD-afflicted brains exhibit an overall decrease in size (Figure 1), and a reduction in glucose uptake that is indicative of decreased neuronal activity. Symptoms include short-term memory loss, confusion, and irritability, which progress to long-term memory deficits and withdrawal from social interactions, followed by a loss of higher cognitive function and finally, death.

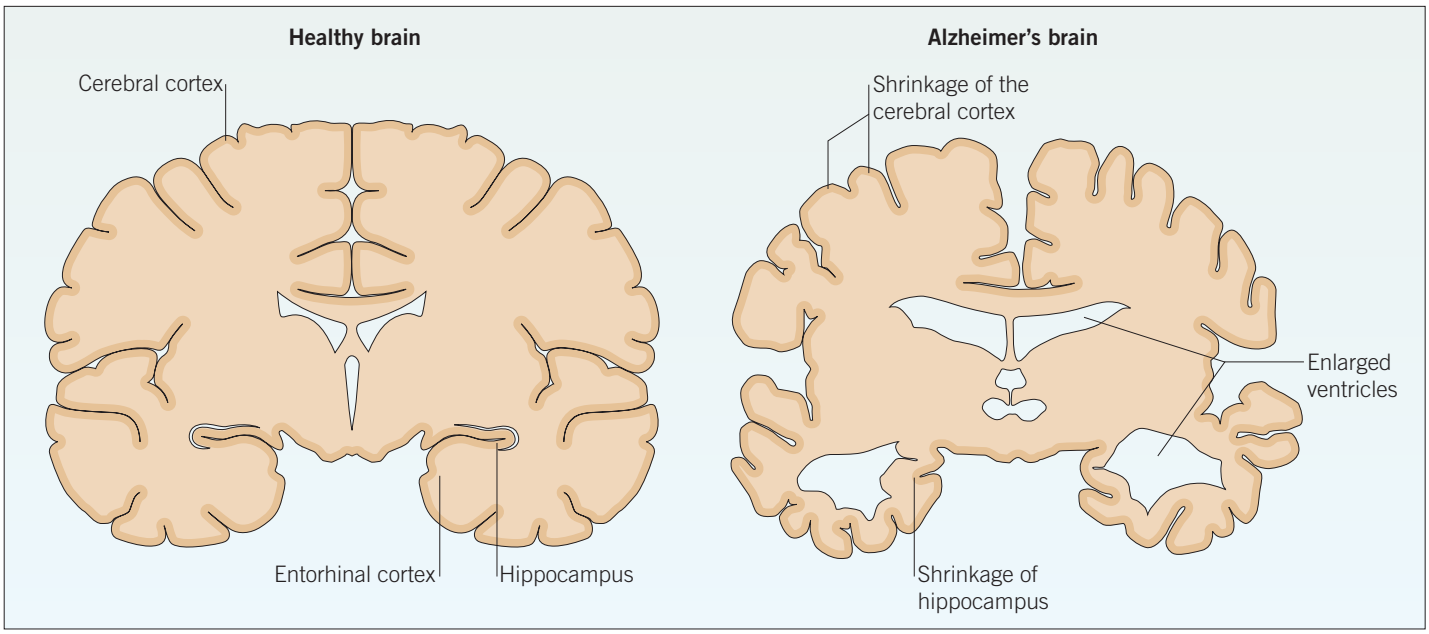
The disease was first described as presenile dementia in 1906 by German psychiatrist Alois Alzheimer. Alzheimer observed a patient with a progressive loss of cognitive function and noticed a peculiar substance in the cortex of the patient's brain post-mortem. Subsequently it was discovered that these extracellular deposits, known as senile plaques, were composed of aggregated proteins called amyloid beta (Aβ). There is no cure for AD, with current therapeutic strategies only alleviating AD-associated symptoms. Drug discovery over the last 10 years has turned towards the development of disease-modifying drugs, in the hope that progression of AD can be slowed.

The causes of AD are not well defined and therefore there are several hypotheses that aim to explain the initiation and progression of the disease.

The Amyloid Hypothesis

A progressive appearance of amyloid plaques in the brain, one of the key pathological hallmarks of AD, forms the basis of the amyloid hypothesis. This hypothesis suggests that

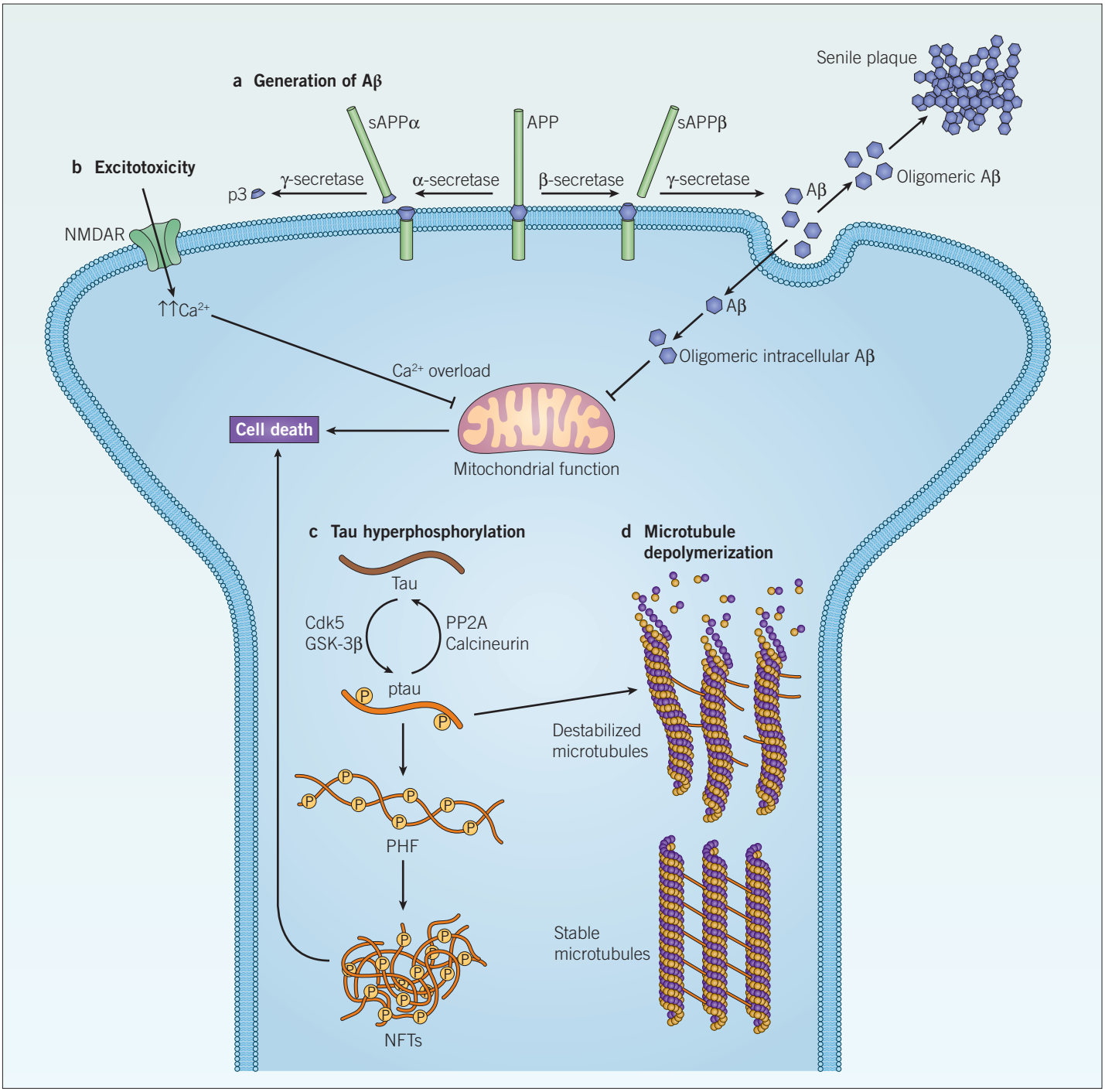
Figure 1 | The Alzheimer's brain



On the left is a normal healthy brain and on the right is a brain with advanced Alzheimer's disease. The Alzheimer's brain exhibits extreme shrinkage of the cerebral cortex (involved in language and emotion), severely enlarged ventricles and shrinkage of the hippocampus (involved in memory).

aggregates of Aβ are the pathogenic agents in AD, which initiate harmful physiological changes leading to neurodegeneration. Amyloid plaques are dense insoluble deposits of Aβ, which are found outside neurons. An increased prevalence of plaques is described throughout the normal brain with aging; in AD patients, however, it is thought that there may be more plaques concentrated in specific regions or increased plaque susceptibility.

Figure 2 | APP processing and tau phosphorylation



(**a**) Amyloid precursor protein (APP) is processed by two pathways. In the non-amyloidogenic pathway: α-secretase cleaves APP within the amyloid beta (Aβ) domain, preventing Aβ formation. In the amyloidogenic pathway: β-secretase and γ-secretase release Aβ intraneuronally, before it is exported from the neuron and aggregates to form senile plaques. (**b**) Excessive activation of NMDA receptors leads to elevated intracellular calcium, which overloads the mitochondria, leading to cell death by excitotoxicity. (**c**) Hyperphosphorylation of tau generates ptau, which forms paired helical filaments (PHF) and further aggregates into neurofibrillary tangles (NFTs). (**d**) In tauopathies, hyperphosphorylation of tau leads to dissociation from microtubules causing them to depolymerize and breakdown, disrupting neuronal function.

Alzheimer's Disease – continued

Secretases

Aβ is the product of proteolysis of a larger transmembrane protein called amyloid precursor protein (APP). Cleavage of APP is by three enzymatic proteases: α-secretase, β-secretase, and γ-secretase. There are two potential outcomes as a result of APP cleavage. One process generates a non-toxic peptide called p3 via cleavage of APP by α-secretase and γ-secretase. Cleavage of APP by β-secretase and γ-secretase leads to the production of insoluble Aβ protein that deposits into plaques (Figure 2a). Different fragments of Aβ can be produced; however, it is the Aβ fragment of 42 amino acids in length, known as Aβ42, that is largely found in plaques. Treating neuronal cultures with Aβ peptides such as **Aβ1-42** (Cat. No. 1428) and **Aβ1-40** (Cat. No. 1191), is useful for studying the vulnerability of neurons to neurodegeneration and understanding the progression of the disease.

The proteases involved in cleavage of APP are of particular interest as they are central to the generation and modulation of the Aβ peptide and can be targeted by small compounds *in vitro* and *in vivo*. β-secretase is therefore an attractive target for the development of inhibitors to treat AD, as this protein functions at the first step in the pathway leading to production of Aβ. Despite a limited number of specific drugs for this target, **EGCG** (Cat. No. 4524) exhibits inhibition of both β-secretase and amyloid assembly. With γ-secretase acting as the final step in the production of Aβ, the development of γ-secretase inhibitors is seen to be a key goal in targeting build-up of toxic Aβ. First generation γ-secretase inhibitors had harmful side-effects due to off-target effects on Notch signaling. However second generation γ-secretase inhibitors, developed to be Notch-sparing – such as **begacestat** (Cat. No. 4283) – have shown more favorable results.

Aβ aggregation

Targeting Aβ oligomerization and aggregation is another strategy for the prevention of Aβ plaque formation. **SEN 1269** (Cat. No. 4699) is a neuroprotective small molecule that directly binds Aβ1-42 to block Aβ aggregation and protect against Aβ1-42-induced neuronal cell death. The compound is also active *in vivo*, reducing the deficits in memory and LTP induced by Aβ oligomers. **CGP 52411** (DAPH, Cat. No. 3360) and **Ro 90-7501** (Cat. No. 2408) are both able to inhibit Aβ42 fibril formation, and therefore reduce Aβ-induced neuronal toxicity, while **MRK 560** (Cat. No. 4000) attenuates Aβ plaque deposition. The neuroprotective compounds **CEP 1347** (Cat. No. 4924) and **colivelin** (Cat. No. 3945) can also protect against the neurotoxic effects of Aβ. CEP 1347 is a JNK inhibitor that protects against Aβ-induced cortical neuron apoptosis, while colivelin suppresses Aβ-induced neuronal cell death and ameliorates memory impairment in AD models *in vivo*. The antioxidant **curcumin** (Cat. No. 2841) also demonstrates the ability to attenuate Aβ aggregation.

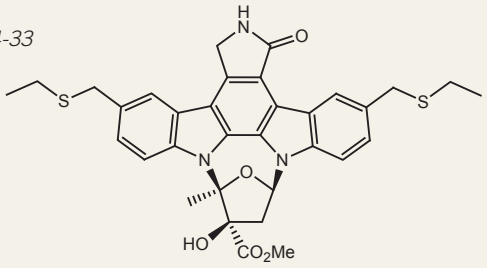
Recent evidence indicates that Aβ deposits probably precede and induce neuronal death, therefore monitoring of the pathology before clinical symptoms present would aid AD diagnosis. Fluorescent probes and dyes including: **K 114** (Cat. No. 3144), a fluorescent dye that detects Aβ, α-synuclein and tau *in situ*; **CRANAD 2** (Cat. No. 4803) a near-infrared probe that undergoes a fluorescence intensity increase upon interacting with Aβ aggregates; and **methoxy-X04** (Cat. No. 4920), a probe that

Box 1: Aβ Aggregation

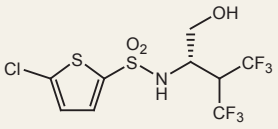
A full list of targets and related products are listed on pages 24-33

Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-Val-His-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-Val-Gly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala

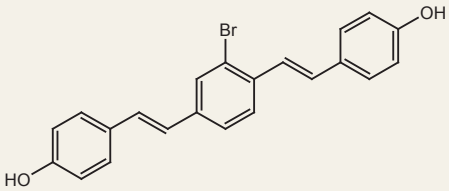
Amyloid β-Peptide (1-42) (human) (1428)
Predominant amyloid β-protein fragment



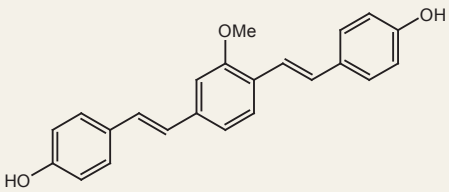
CEP 1347 (4924)
Blocks Aβ-induced cortical neuron apoptosis



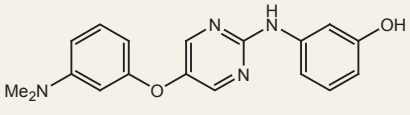
Begacestat (4283)
γ-secretase inhibitor



K 114 (3144)
Amyloid fibril-specific fluorescent dye



Methoxy-X04 (4920)
Fluorescent amyloid β detector; brain penetrant



SEN 1269 (4699)
Amyloid-β aggregation inhibitor

allows the detection of plaques, tangles and cerebrovascular amyloid *in situ*, are all tools that will enable detection, quantification and characterization of amyloid plaques in different model systems (Box 1).

Mitochondrial dysfunction

Mitochondrial dysfunction is implicated in Aβ-induced neuronal toxicity in AD. Overproduction of mitochondrial reactive oxygen species (ROS) and increased oxidative stress is evident in the brains of AD patients. Disruption in energy metabolism, enzyme function and the mitochondrial membrane permeability transition pore (mPTP) all lead to mitochondrial dysfunction, often as a result of progressive accumulation of mitochondrial Aβ. Toxicity in the mitochondria therefore ultimately leads to cell death (Figure 2). It is thought that mitochondrial dysfunction, especially that leading to compromised energy production, precedes the toxic accumulation of plaques and therefore may play an early role in the pathogenesis of AD. **Methylene blue** (Cat. No. 3213), an inhibitor of tau aggregation, has also been shown to prevent mitochondrial dysfunction and targets some of the mechanisms that are impaired in AD brains, such as aerobic respiration. **Dimebon** (Cat. No. 3201), which has known neuroprotectant properties against β-amyloid neurotoxicity, has also been suggested to stabilize mitochondrial function and inhibit cell death.

Tau Hypothesis

Deposition of neurofibrillary tangles composed mainly of misfolded hyperphosphorylated tau (ptau) aggregates is the second major hallmark of AD. The tau hypothesis describes the following neuropathogenesis: hyperphosphorylated tau begins to pair with other threads of tau, eventually forming neurofibrillary tangles inside neuron cell bodies. Neurofibrillary tangles are deposited in a systematic fashion, correlating closely with cognitive decline.

Tau gives structural stability to microtubules that act as dendrite scaffolding, maintaining the shape of the neuron and contact between neurons. The binding of tau to microtubules is modulated by kinases and phosphatases; phosphorylation detaches it from microtubules, which affects axonal trafficking. An imbalance between kinase and phosphatase activities results in the accumulation and aggregation of chronically hyperphosphorylated tau (Figure 2c). Although the cause of this imbalance is unclear, several candidate enzymes have been identified that are likely to contribute to these events, some of which are discussed below.

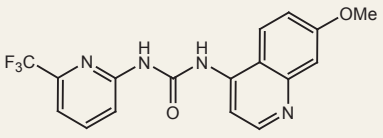
Kinases

The abnormal phosphorylation of tau evident in AD has driven researchers to identify the kinases involved, in order to develop effective kinase inhibitors. Kinases that have been identified include glycogen synthase kinase-3 (GSK-3), dual-specificity tyrosine-phosphorylation-regulated kinase (DYRK)1A, cyclin-dependent kinase 5 (cdk5), and casein kinase 1 (CK1).

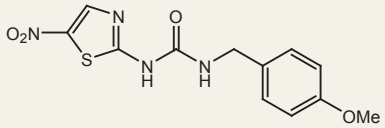
Early studies demonstrated that treatment of cultured neurons with Aβ fibrils induced tau phosphorylation and that this increase was sensitive to **lithium** (Cat. No. 4740), which is known to inhibit GSK-3. Inhibitors such as **indirubin-3′-oxime** (Cat. No. 1813), which inhibit GSK-3β as well as cdk5, have been shown to diminish tau phosphorylation. Maleimides such as **SB 415286** (Cat. No. 1617) and **SB 216763** (Cat. No.

Box 2: GSK-3β

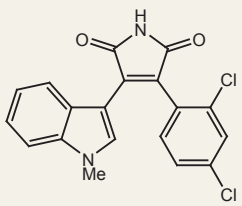
A full list of targets and related products are listed on pages 24-33



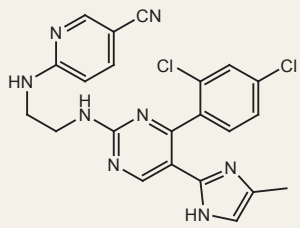
A 1070722 (4431)
Highly potent, selective GSK-3 inhibitor



AR-A 014418 (3966)
Selective GSK-3 inhibitor



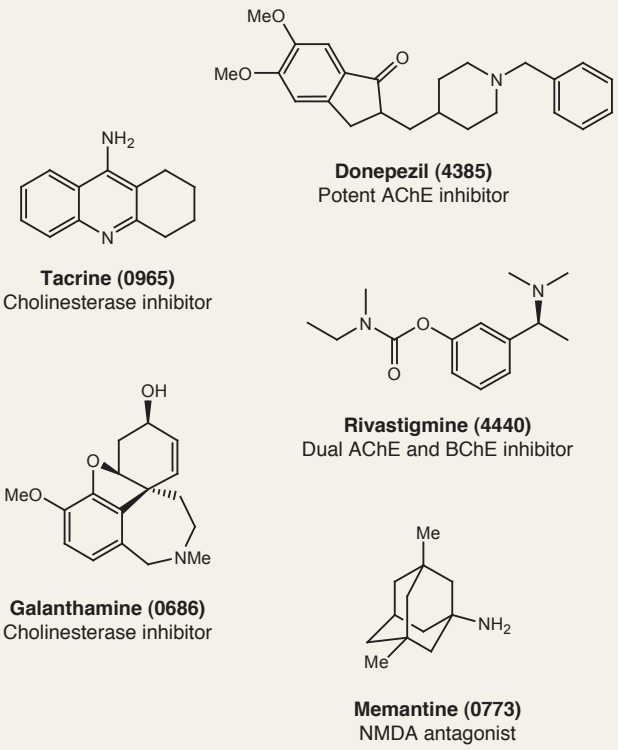
SB 216763 (1616)
Potent, selective GSK-3 inhibitor



CHIR 99021 (4423)
Highly selective GSK-3 inhibitor;
HCl salt also available (Cat. No. 4953)

Box 3: Current Therapeutics for Alzheimer's Disease

A full list of targets and related products are listed on pages 24-33



1616) show selectivity for GSK-3, with the latter demonstrating an ability to reduce tau phosphorylation in postnatal rats and to reverse Aβ-induced tau phosphorylation (Box 2). Thiazoles such as **AR-A 014418** (Cat. No. 3966) compete with ATP for binding to GSK-3β, and have been shown to reduce tau phosphorylation and aggregation in a mouse model of tauopathy. Upregulation of CK1 mRNA is evident in brain samples from subjects with AD. CK1 inhibitors such as **D 4476** (Cat. No. 2902) cause a significant and dose-dependent reduction in Aβ40 and Aβ42 production *in vitro*. Additionally **(*R*)-DRF053** (Cat. No. 3610), a dual cdk/CK1 inhibitor, has demonstrated an ability to inhibit Aβ production.

Phosphatases

Protein phosphatases catalyze the removal of phosphate groups from target proteins. Consequently, they are targets of interest with regard to the aberrantly high levels of tau phosphorylation observed in AD. The activity of the serine/threonine protein phosphates PP1, PP2A and PP5 have been shown to be decreased in AD brains. A significant amount of research has been focused on PP2A, the phosphatase thought to be mainly responsible for ptau dephosphorylation. Strategies to target dysregulation of protein phosphatase activity using compounds such as **ceramide** (Cat. No. 0744), a serine/threonine protein phosphatase activator, have been demonstrated to promote PP2A activity. **Memantine** (Cat. No. 0773) has also been reported to elevate hippocampal PP2A activity and decrease tau phosphorylation both in cells and in rat brain slices by blocking the interaction of PP2A with I2, an inhibitor binding protein. **Okadaic acid** (Cat. No. 1136) and **calyculin A** (Cat. No. 1336) are protein phosphatase inhibitors that have been suggested to have an additional role in AD, as they were able to stimulate secretion of APP.

Microtubules

As a result of the generation of hyperphosphorylated tau, accumulation of neurofibrillary tangles and microtubule instability leads to the breakdown of neuronal function (Figure 2d). Microtubule stabilizing agents such as **taxol** (Cat. No. 1097) have been used to prevent breakdown in microtubules associated with tau hyperphosphorylation. Several classes of compounds have now been identified that inhibit tau aggregation and/or disassemble existing filaments *in vitro*. Phenothiazines, including **methylene blue** (Cat. No. 3213), inhibit tau filament formation and have also been reported to attenuate the rate of cognitive decline in AD patients. A new formulation of methylene blue, with higher bioavailability, is also now undergoing phase III trials. Anthraquinones, such as the chemotherapeutics **daunorubicin** (Cat. No. 1467) and **doxorubicin** (Cat. No. 2252), have also been identified as inhibitors of tau aggregation. Alternative strategies to reduce the amount of tau in neurons involve enhancing degradation of phosphorylated tau, which has been illustrated by inhibiting heat shock protein 90 (Hsp90) using the geldanamycin derivative, **17-AAG** (Cat. No. 1515). This reduces the burden of phosphorylated tau in affected brain regions. Interestingly, 17-AAG shows preferential affinity for complexes associated with misfolded proteins, suggesting that 17-AAG may not interfere with other physiologically important Hsp90-client protein interactions.

Cholinergic Hypothesis

The cholinergic system is a key modulator of excitatory amino acid (EAA) neurotransmission. Deficits in EAA neurotransmission are associated with a decline in learning and memory, which led researchers to postulate that the cholinergic system may play a role in the cognitive decline evident in AD. The cholinergic hypothesis of AD is one of the earliest theories; it proposes that AD is caused by deficits in the enzymes responsible for the synthesis of acetylcholine (ACh). Drugs that inhibit cholinesterases, the enzymes responsible for the breakdown of ACh in the synaptic cleft, displayed efficacy in delaying the symptoms of AD and received FDA and European approval, of which **tacrine** (Cat. No. 0965) was the first. However, second generation cholinesterase inhibitors including **donepezil** (Cat. No. 4385), **rivastigmine** (Cat. No. 4440) and **galanthamine** (Cat. No. 0686; Figure 3) have demonstrated a more favorable clinical profile (Box 3). **Galanthamine** has shown promise in treating the deficit in cholinergic signaling because of its dual effect on cholinergic synapses, both as an allosteric

Figure 3 | *Lycoris radiata* – a source of galanthamine

The red spider lily (*Lycoris radiata*) is a source of galanthamine, a drug currently approved for the treatment of mild to moderate Alzheimer's disease.

potentiator of nAChRs and as an anticholinesterase. Long-term administration has recently been suggested to reduce APP deposition and neurodegeneration in a mouse model of AD, suggestive of a potential role for this target in disease-modifying treatment. For AD sufferers, however, these drugs largely offer symptomatic relief without modifying the course of the disease.

Theory of Excitotoxicity

Glutamate-mediated neurotoxicity is a common theme in neurodegenerative diseases such as Parkinson's and Huntington's disease, and has also been implicated in the pathogenesis of AD. Excitotoxicity resulting from excessive activation of NMDA receptors has been suggested to enhance the localized vulnerability of neurons in a manner consistent with AD neuropathology (Figure 2b). Attempts to develop drugs that blocked the action of glutamate were unsuccessful in the beginning, since these receptors are also required for normal brain function. It was a major breakthrough when **memantine** (Cat. No. 0773; Box 3) was discovered to have beneficial effects in AD, blocking excessive glutamate excitotoxicity that leads to cell death without affecting normal glutamate signaling. Memantine blocks NMDA-type glutamate receptors and represents the first in this class of AD medications.

Emerging Targets

5-HT receptors

Extensive serotonergic denervation has been observed in the AD brain and the involvement of 5-HT in both cognition and behavioral control has made its receptors an attractive target. Positive results have been noted in animal models of memory using the high affinity 5-HT_6 antagonist **BGC 20-761** (Cat. No. 3326; Box 4). Despite 5-HT receptors being unlikely to alter the progression of the disease, 5-HT_4 receptors have been suggested to play a role in the regulation of Aβ; therefore inhibitors such as **GR 113808** (Cat. No. 1322) and **GR 125487** (Cat. No. 1658), which selectively target the 5-HT_4 receptor, may be useful in characterizing its role in AD.

Cannabinoid receptors

Alterations in components of the cannabinoid system have been reported in brains obtained from Alzheimer's patients. Cannabinoids are neuroprotective against excitotoxicity, and have also been shown to protect neurons from the deleterious effects of Aβ and ptau. Senile plaques in AD patients express the cannabinoid receptors CB_1 and CB_2; intracerebroventricular administration of synthetic cannabinoids such as **WIN 55,212-2** (Cat. No. 1038), **HU 210** (Cat. No. 0966; Box 4) and the CB_2 agonist **JWH 133** (Cat. No. 1343) have shown potential in blocking Aβ-induced microglial activation, cognitive impairment, and loss of neuronal markers in rats.

Dual-specificity tyrosine-phosphorylation-regulated kinase

Dual-specificity tyrosine-phosphorylation-regulated kinase (DYRK)1A overexpression has been suggested to be a significant factor leading to cognitive deficits in people with Alzheimer's disease (AD). It has been suggested that DYRK1A may provide a link between aberrant amyloid and tau pathology in AD. Dyrk inhibitors such as **INDY** (Cat. No. 4997; Box 4) have been shown to reverse aberrant tau-phosphorylation, with **proINDY** (Cat. No. 4998), a prodrug of INDY, displaying effectiveness *in vivo*. These recent studies suggest that DYRK1A is a promising target for AD, as investigators search for alternatives to β-secretase and γ-secretase.

Protein O-GlcNAcase

Protein *O*-GlcNAcase is a hydrolase involved in tau phosphorylation. Studies, using the selective inhibitor, **thiamet G** (Cat. No. 4390; Box 4), showed decreased tau phosphorylation and neurodegeneration *in vivo*, making protein *O*-GlcNAcase an emerging therapeutic target for slowing the progression of AD.

Oxidative stress

Oxidative stress is apparent in the early stages of neurodegenerative diseases, and is suggested to precede the appearance of neurofibrillary tangles in AD. Some adverse effects of Aβ

appear to be mediated by free radical formation and a resultant oxidative imbalance. Therefore, the free radical-scavenging properties of antioxidants such as vitamin E and **L-ascorbic acid** (Vitamin C, Cat. No. 4055), as well as **melatonin** (Cat. No. 3550), may be beneficial in inhibiting the toxic effect of Aβ. The antioxidant coenzyme **Q10** (Cat. No. 3003) has been shown to preserve mitochondrial membrane potential during oxidative stress, and protects neuronal cells by attenuating Aβ overproduction and intracellular Aβ plaque deposits.

Retinoic acid receptors

The retinoic acid receptor (RAR)α plays a key role in homeostatic control of synaptic plasticity, which is essential for memory function. It has been shown that RARα signaling is downregulated by Aβ, which inhibits the synthesis of retinoic acid. RARα signaling improves cognition and promotes Aβ clearance in Tg2576 mice (mice expressing mutant APP), as demonstrated by the use of the selective RARα agonist, **AM 580** (Cat. No. 0760).

Stem cell therapy

Research into AD using stem cell therapy has been limited in comparison to Parkinson's and Huntington's disease, due to the widespread loss of neurons observed in AD. One approach is to transplant neural stem cells; however, for this cell replacement strategy to be successful, the cells would need to migrate to different areas across the brain, and differentiate into functional neuronal subtypes that establish connectivity with existing neurons. This is difficult to achieve.

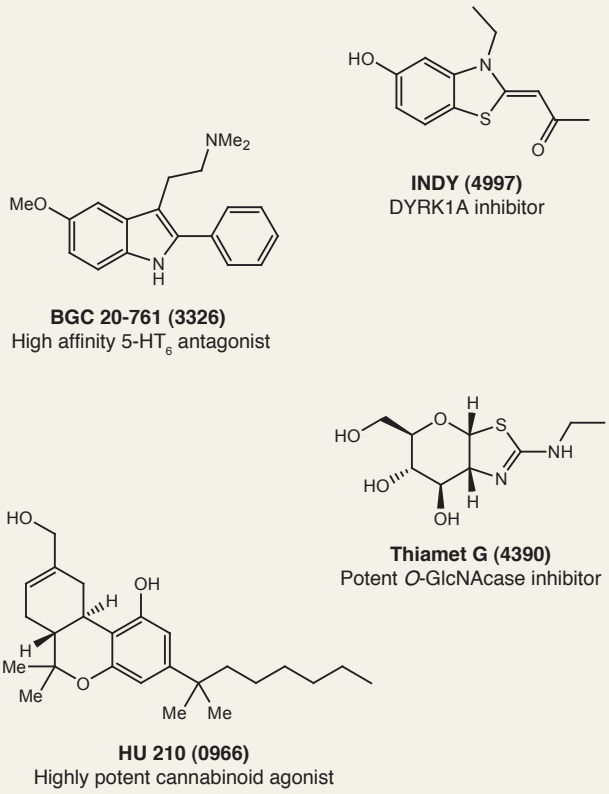
Nevertheless, studies with neural stem cells (NSCs) have highlighted a neuroprotective function: NSCs improve cognition and reduce neuronal loss *in vivo*, without directly replacing affected neurons. These NSCs express neurotrophins that may help modulate neuronal survival. For more information on stem cell therapy for neurodegenerative disorders, see page 21.

Future Directions

Current treatments for AD alleviate the symptoms of the disease, however they do not modify its natural progression. Disease-modifying approaches have recently become the focus of Alzheimer's disease research. Despite the prominence of particular theories on the pathogenesis of AD, there are aspects of each theory that cannot fully explain the degenerative effects of AD. Pathological targets such as the cholinesterases, amyloidogenic secretases, Aβ aggregation, and tau phosphorylation and fibrillation are the primary targets researchers are currently exploring. The hope is that new targets will be revealed that will enable identification of drugs to combat the degenerative nature of the disease.

Box 4: Emerging Targets for Alzheimer's Disease

A full list of targets and related products are listed on pages 24-33



Parkinson's Disease

Products by Category	Page

Introduction

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). The degenerating neurons typically contain 'Lewy bodies' and 'Lewy neurites'– the result of abnormal α-synuclein aggregation within the neuron (Figure 4). Together this leads to symptoms of tremor, bradykinesia, rigidity and postural instability, whilst further neurological changes trigger a number of more complex and variable nonmotor symptoms.

The pathogenesis of PD has been proposed to be multifactorial, with mitochondrial dysfunction, α-synuclein aggregation and proteasome dysregulation being cited as major drivers behind the loss of dopaminergic neurons in PD. Analysis of gene expression in PD patients has also revealed a genetic component of the disease, with mutations in a number of genes – including *PINK1*, *LRRK2*, *DJ-1*, *SNCA* and *ATP13A2*, amongst others – being linked to the development of PD. Proteins encoded by these genes are therefore under investigation to determine their influence on the pathogenesis of PD. Although there remains a greater proportion of sporadic cases with no obvious genetic component, analysis of these PD-associated genes has provided significant advances in understanding the pathogenesis of the disease.

In addition to targeting the underlying pathophysiological changes associated with PD, drug discovery programs also aim to develop effective therapies for the side effects of PD treatment, particularly dyskinesias invoked by L-DOPA treatment. Dopamine and glutamate receptors are long-established targets for treating L-DOPA-induced dyskinesias, while newer targets, including PARP-1, 5-HT and adenosine receptors, are also under investigation.

Etiology of Parkinson's Disease

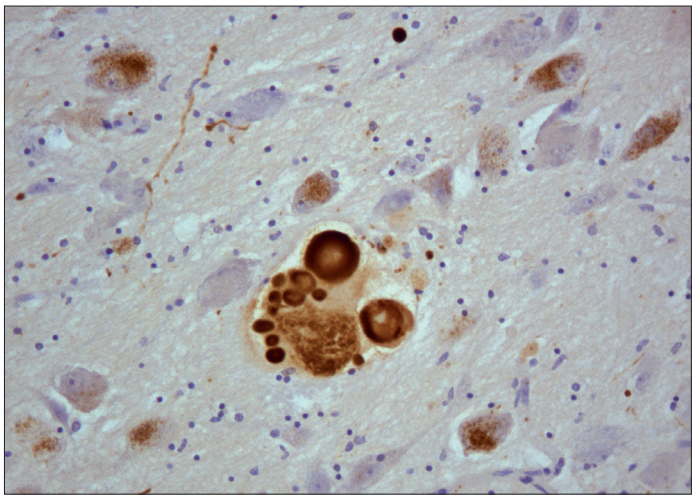
The characteristic motor symptoms of PD occur as a result of the death of dopaminergic neurons in the SNc, a constituent of the basal ganglia. The basal ganglia are a collection of nuclei within the brain (Figure 5a) that are integral to controlling motor function, learning and cognition. In the basal 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, leading to an increase in motor activity. In PD patients the loss of dopamine neurons within the basal ganglia leads to a decrease in motor activity (Figure 5b).

Dopamine signaling within the basal ganglia is also modulated by cholinergic interneurons within the striatum and by serotonergic neurons from the dorsal raphe nucleus (DR). As a result, both serotonergic and cholinergic neurons are also under investigation as potential non-dopaminergic targets for the treatment of PD.

Mitochondrial Dysfunction

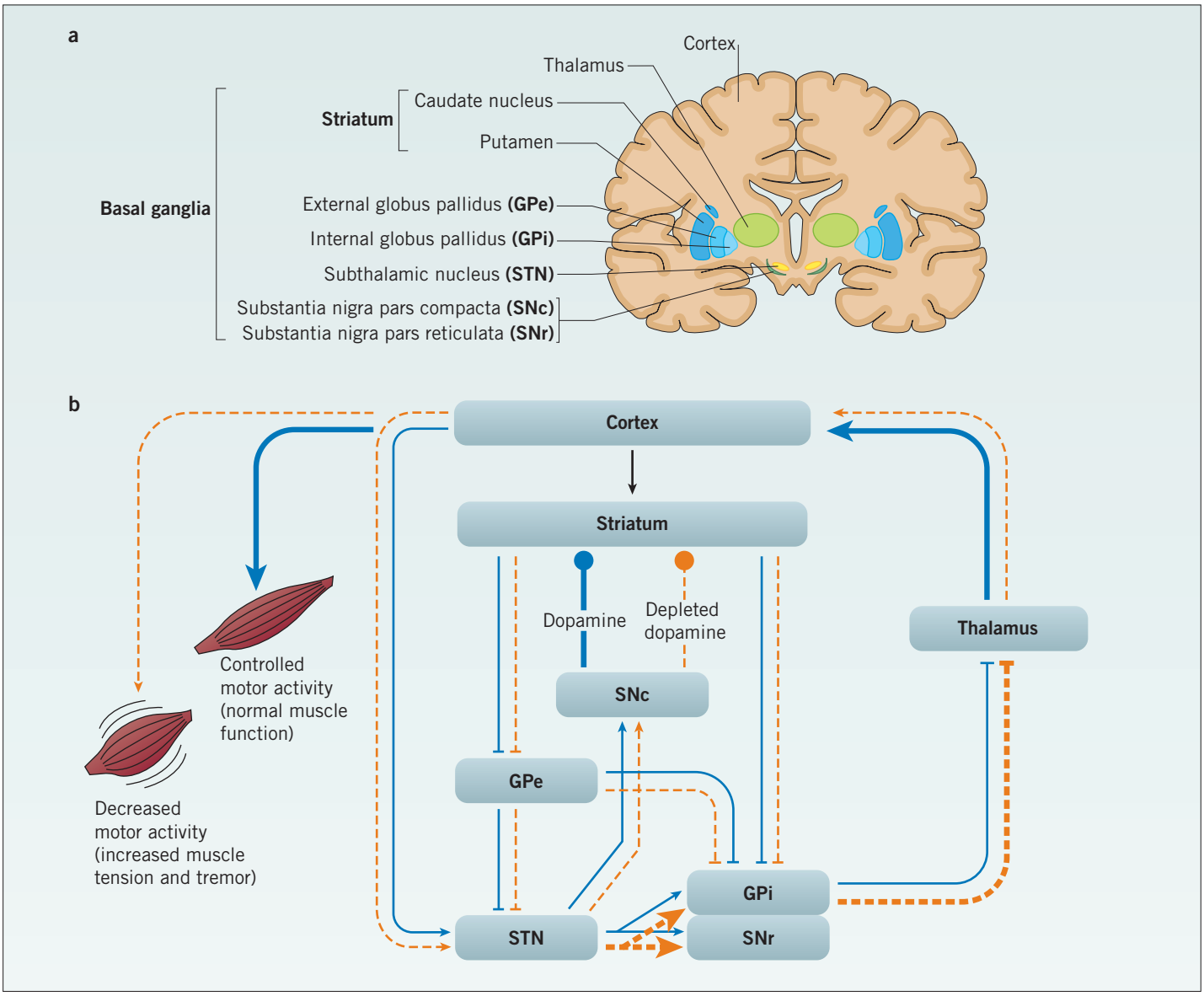
It is thought that the selective death of dopaminergic neurons in PD is linked to an increased vulnerability of these neurons to external cell death-inducing stimuli. This is exemplified in the response of nigrostriatal dopaminergic neurons to the mitochondrial complex I inhibitor **rotenone** (Cat. No. 3616); although rotenone is distributed uniformly throughout the brain following administration, the development of cytoplasmic inclusions and subsequent neuronal death selectively

Figure 4 | Lewy bodies



Insoluble aggregates of α-synuclein – 'Lewy bodies' – within a brain tissue sample of a patient with Parkinson's disease. Image reproduced with kind permission of Professor Stephen Gentleman, Imperial College London.

Figure 5 | The basal ganglia



(**a**) The anatomical location of regions of the basal ganglia. Abbreviations used in the diagram are highlighted in bold. (**b**) This simplified diagram illustrates the pathways in the basal ganglia that control motor function. Under normal conditions a balance in the circuitry provides controlled movement. Dopamine secreted from neurons within the substantia nigra pars compacta (SNc) (indicated by circle arrows) modulates neurotransmission through different networks within the basal ganglia; the end result is moderation of thalamic input to the motor cortex, through excitatory and inhibitory signaling. This facilitates controlled motor activity. In PD, however, dopaminergic neurons within the substantia nigra are lost, leading to depletion of dopamine. This leads to an imbalance in these pathways, which results in decreased initiation of movement and an increased inhibition of movement, ultimately leading to decreased motor activity. Blue arrows represent the normal circuitry, with dashed orange arrows illustrating the effect of decreased dopamine input at the striatum. Thick arrows represent increased input.

affects nigrostriatal dopaminergic neurons. 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 **(*R*)-deprenyl**

(Cat. No. 1095), **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).

Complex I dysfunction in the absence of exposure to complex I inhibitors has also been observed in post-mortem studies of PD brains, suggesting that studying complex I and 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), **Bax inhibitor peptide V5** (Cat. No. 1785) and **iMAC2** (Cat. No. 3794) may be useful for studying these mechanisms. The finding that proteasome inhibitors such as **MG 132** (Cat. No. 1748) exacerbate the toxic effects of complex I inhibition suggests that the proteasome is involved in complex I-mediated neuronal death, and that dysregulated proteasome function may also confer susceptibility to PD. Other proteasome-targeting chemical tools that can be used to probe this include **lactacystin** (Cat. No. 2267), **AM 114** (Cat. No. 2564) and **PSI** (Cat. No. 4045) (Box 6).

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.

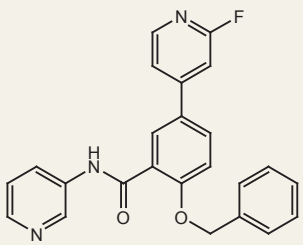
Other mitochondrial proteins postulated to be involved in PD include PINK1, DJ-1, LRRK2 and parkin. These proteins are either located within the mitochondria or, in the case of parkin, are directly recruited by mitochondrial proteins. Mutations in the genes encoding these proteins are linked to specific forms of PD, and so are under investigation to uncover novel strategies for targeting the disease.

In particular, results of recent drug discovery programs have provided experimental tools for studying LRRK2, a protein kinase which has been implicated in both sporadic and familial PD. The most common LRRK2 mutation observed in PD is G2019S, a mutation which affects the kinase domain of LRRK2 and is thought to increase its autophosphorylation activity. LRRK2 associates with α-synuclein and this interaction has been proposed to increase the size of α-synuclein-containing intracytoplasmic inclusions. The potent and selective LRRK2 inhibitors **GSK2578215A** (Cat. No. 4629), **LRRK2-IN-1** (Cat. No. 4273) and **CZC 54252** (Cat. No. 4534) will enable further research into the function of LRRK2 and may shed light on the extent of its involvement in PD (Box 5).

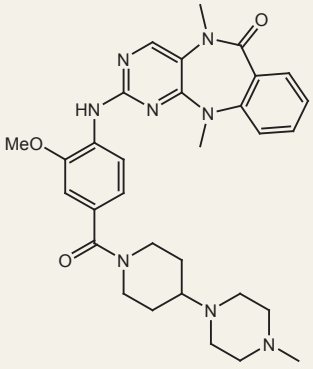
Parkin, a ubiquitin ligase that is mutated in juvenile onset PD, is also a potential new therapeutic target for PD. In patients with parkin mutation-associated or sporadic PD, the parkin substrate AIMP2 accumulates in neurons, triggering PARP-1 activation. PARP-1 is a crucial component of the DNA damage

Box 5: LRRK2

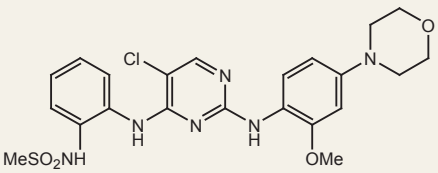
A full list of targets and related products are listed on pages 24-33



GSK2578215A (4629)
Potent, selective LRRK2 inhibitor; brain penetrant



LRRK2-IN-1 (4273)
Potent and selective LRRK2 inhibitor



CZC 54242 (4534)
Potent LRRK2 inhibitor; neuroprotective

response, yet its excessive activation has been linked to a mechanism of cell death termed 'parthanatos.' Blocking neuronal PARP-1 activity has been proposed to counteract this pathway and may provide neuroprotection in PD. Brain penetrant PARP-1 inhibitors, including **PJ 34** (Cat. No. 3255) and **DR 2313** (Cat. No. 2496) may be useful tools (Box 6).

Depletion of Dopaminergic Signaling

The death of dopaminergic neurons has severe effects on motor function due to the involvement of dopamine in increasing motor activity (Figure 5b). In order to address the decreased dopamine availability in PD, treatment has classically involved administering **L-DOPA** (Cat. No. 3788; Box 7), a precursor to dopamine that (unlike dopamine) can cross the blood-brain barrier. This line of treatment is still the most widely used, but its metabolism *in vivo* is associated with a number of unwanted side-effects including dyskinesias. L-DOPA-induced dyskinesias (LID) remains a significant problem for PD patients despite L-DOPA being accepted as a 'gold standard' for the treatment of PD. Research into alternative methods of increasing dopamine signaling in the brain may provide a replacement therapy for L-DOPA with fewer side effects.

The availability of L-DOPA is negatively affected by the activity of catechol *O*-methyltransferase (COMT) and dopa decarboxylase (DDC) and therefore co-administering inhibitors of these enzymes with L-DOPA is thought to increase L-DOPA's efficacy. COMT inhibitors such as **entacapone** (Cat. No. 4720) and **OR-486** (Cat. No. 0483) 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) and **L-(-)-α-methyldopa** (Cat. No. 0584) 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) (Box 7). These mimic the effects of the depleted dopaminergic neurons within the basal ganglia and improve motor function. However, 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.

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 serotonergic neurons are also depleted in PD patients. Experimental tools for 5-HT receptors, in particular agonists such as **8-hydroxy-DPAT** (Cat. No. 0529), **tandospirone** (Cat. No. 2854), **xaliproden** (Cat. No. 2491) and **S 14506** (Cat. No. 1771) may enable researchers to determine the influence of 5-HT on PD.

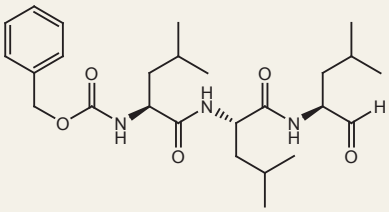
Adenosine A_{2A} receptors are also a potential target for new PD therapeutics since these receptors co-localize with dopamine D_2 receptors in the striatum where they inhibit dopaminergic signaling. Inhibiting A_{2A} receptor activity therefore removes this effect and enhances D_2 receptor activity. This effect of normalizing dopamine signaling can be produced experimentally using A_{2A} antagonists such as **SCH 58261** (Cat. No. 2270), **ANR 94** (Cat. No. 3937) and **ZM 241385** (Cat. No. 1036) (Box 7).

α-Synuclein

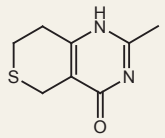
Dopaminergic neurons in PD commonly contain aggregates of α-synuclein, a protein with an undetermined function that is predominantly found in neuronal tissue. The gene encoding α-synuclein, *SNCA*, is mutated in some forms of PD, and these mutations are thought to promote α-synuclein oligomerization and fibrillogenesis. α-synuclein has therefore been the focus of considerable PD research. A key feature of α-synuclein found within PD brains is that it is selectively and extensively phosphorylated at Ser129, a characteristic that has been shown to

Box 6: Proteasome and PARP

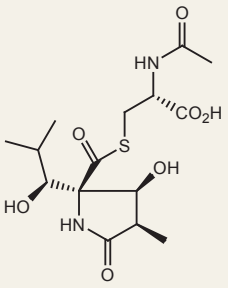
A full list of targets and related products are listed on pages 24-33



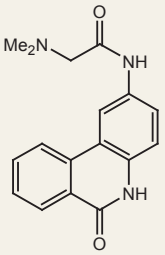
MG 132 (1748)
Proteasome and calpain inhibitor



DR 2313 (2496)
PARP-1 and PARP-2 inhibitor



Lactacystin (2267)
Cell-permeable, potent and selective proteasome inhibitor



PJ 34 (3255)
Potent PARP inhibitor

increase α-synuclein toxicity. Kinases implicated in α-synuclein Ser129 phosphorylation include casein kinase 1 (CK1), casein kinase 2 (CK2) and GRK2, amongst others. Therefore, targeting these kinases using inhibitors such as **D 4476** (Cat. No. 2902), **TBB** (Cat. No. 2275) and **GRK2i** (Cat. No. 3594) blocks Ser129 phosphorylation and may retard 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 paradoxical, is thought to exert a protective effect in PD by reducing the presence of toxic early aggregation intermediates such as oligomers. This can be induced experimentally using **B2** (Cat. No. 2855), a neuroprotective compound that has proven effects in animal models of neurodegeneration.

Stem Cells

Neurons derived from stem cells have been used for drug screening and cell replacement therapy in neurodegenerative disorders including PD. In addition, the pathogenesis of PD may be modeled using stem cell-derived neurons.

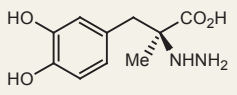
PD has been a focus of significant stem cell research, due to the fact that a specific type of neuron and discrete brain region are involved. Previously, dopaminergic neuroblasts could be replaced by transplant of human embryonic mesencephalic tissue, a source rich in these cells. These grafts served as proof of principle that cell replacement therapy could be an effective way to treat PD in humans. Building upon this idea, pluripotent stem cells may also be directed to differentiate into dopaminergic neuroblasts for cell therapy, constituting a standardized source of cell material. For more information on stem cell therapy for neurodegenerative disorders, see page 21.

Future Directions

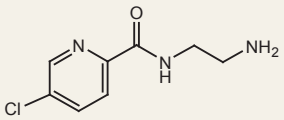
The identification of multiple gene mutations associated with PD has provided a new set of molecular targets for the focus of future PD research, whilst further genetic analysis may uncover additional molecular targets involved in PD. The availability of potent and selective tool compounds, such as LRRK2 inhibitors, will enable researchers to elucidate the contribution of these individual proteins to the pathogenesis of PD and may lead to an efficacious therapy to replace the current gold standard, L-DOPA. Combinatorial therapy, such as the co-administration of dopamine receptor partial agonists with 5-HT agonists, may also represent a beneficial strategy for targeting the multi-faceted nature of PD and may lead researchers to achieve the ultimate goal: an efficacious therapy for PD.

Box 7: Dopaminergic Signaling

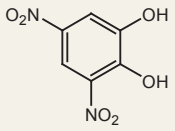
A full list of targets and related products are listed on pages 24-33



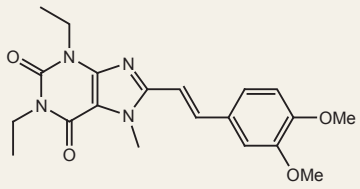
(*S*)-(-)-Carbidopa (0455)
Aromatic L-amino acid decarboxylase inhibitor



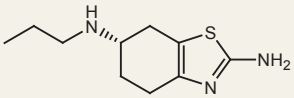
Lazabemide (2460)
Selective MAO-B inhibitor



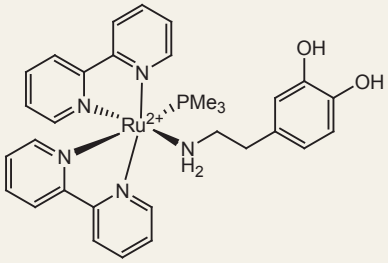
OR-486 (0483)
Catechol *O*-methyltransferase inhibitor



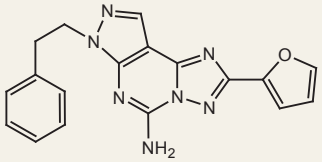
Istradefylline (5147)
Potent and selective adenosine A_{2A} receptor antagonist



Pramipexole (4174)
Selective D_3 agonist



RuBi-Dopa (4932)
Caged dopamine; exhibits two-photon sensitivity



SCH 58261 (2270)
Potent, highly selective A_{2A} antagonist

Huntington's Disease

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease. It is characterized by mental decline, psychiatric disorder and motor dysfunction – predominantly chorea, an involuntary movement disorder. These symptoms are thought to result from the cellular aggregation and activity of mutant huntingtin protein in the cytoplasm and nuclei of neurons. Although huntingtin protein (Htt) is expressed throughout the central nervous system, medium spiny neurons (MSNs) in the basal ganglia of the striatum exhibit particular vulnerability to neurodegeneration in HD. There are no disease-modifying therapies currently available for HD; the only currently FDA-approved drug for HD is **tetrabenazine** (Cat. No. 2175), a reversible inhibitor of vesicular monoamine transporter type 2 (VMAT2). Current research is focused on the identification of new therapeutic targets, some of which are described below.

Etiology of Huntington's Disease

Htt is a predominantly cytoplasmic protein that is vital for embryogenesis and development. It has been linked to a variety of processes, including protein trafficking and vesicle transport; a potential role as a scaffold protein therefore seems likely. Htt is encoded by the *IT15* gene, in which the unstable expansion of a three base sequence (CAG, encoding glutamine) in exon 1 results in the generation of a protein with an elongated stretch of glutamine residues (a polyglutamine (polyQ) tract) at its amino terminus. If more than 35 CAG repeats are present, the protein expressed (mutant huntingtin, mHtt) has different characteristics to the normal protein product. Both mutant and wild-type (wt) alleles are expressed in HD; if more than 40 CAG repeats are present in an allele, it is genetically penetrant. Domains containing multiple glutamine residues are often involved in the mediation of protein-protein interactions, and necessitate a certain degree of inherent conformational flexibility. Mutations affecting this region are thought to affect this flexibility and thus protein activity. mHtt, and fragments of it, initiate both deleterious as well as compensatory processes that leave affected neurons more susceptible to general injury, such as oxidative and excitotoxic stressors.

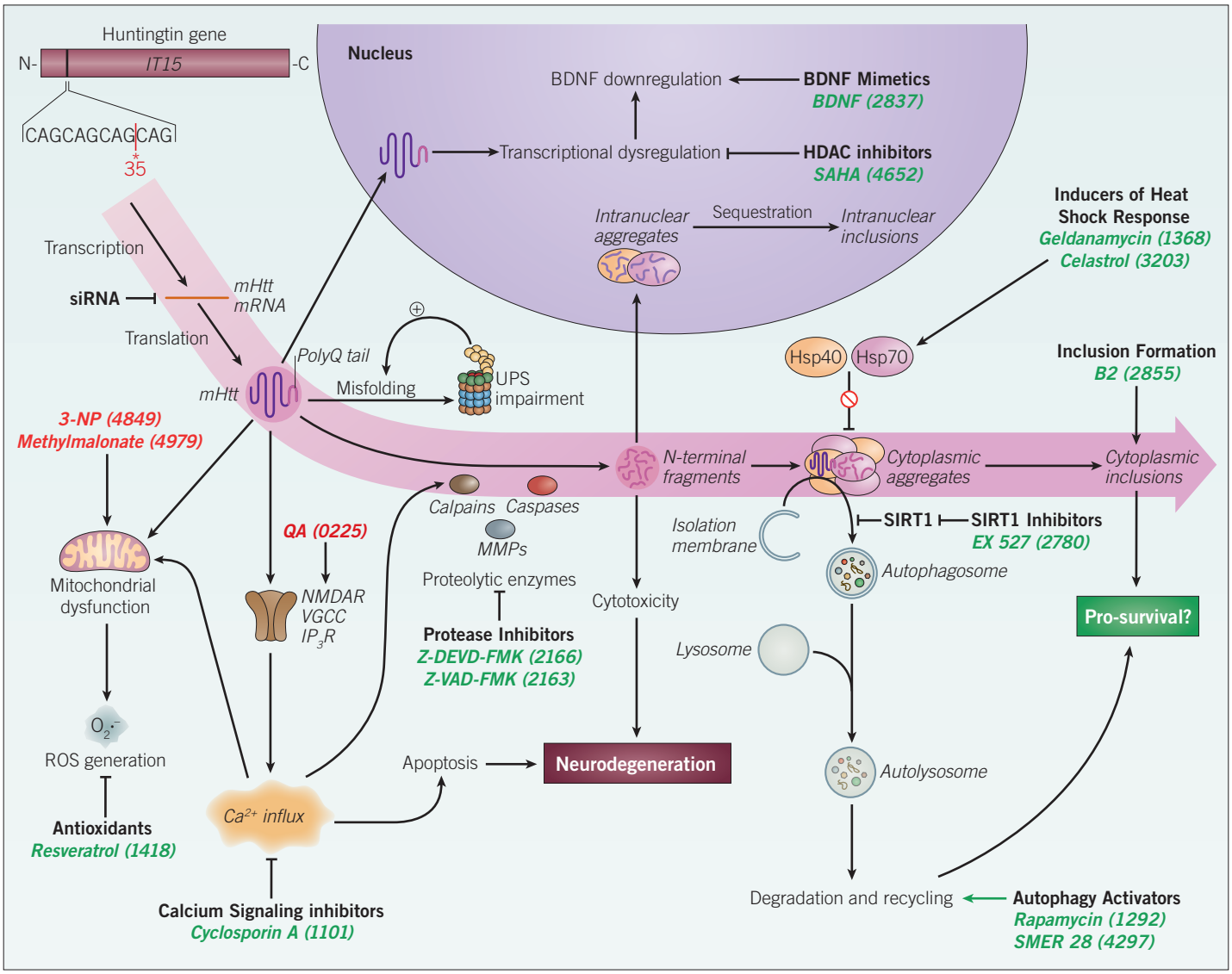
Numerous transgenic *in vivo* and *in vitro* models have been generated to examine the pathology and behavioral phenotypes of HD, with particular focus on motor deficits, intranuclear inclusions, transcriptional dysregulation, mitochondrial dysfunction and excitotoxicity. Using these models as a basis for research into the mechanisms underlying the motor and nonmotor symptoms of HD has proven fruitful; current treatments for HD are, however, unable to offset the progression of the disorder. Nevertheless, treatment of the movement and behavioral disorders associated with HD may mitigate disease symptoms, while regenerative therapies could replace damaged neurons. For a summary of therapeutic interventions in HD, see Figure 6.

Proteolysis and Inclusion Bodies

Inclusion bodies are a pathological hallmark of HD, and are usually observed in cells where mHtt is expressed. They are formed of protein aggregates containing toxic N-terminal mHtt fragments, which are generated by the caspase, calpain and matrix metalloproteinase (MMP) enzymes that are expressed in MSNs. Aggregates also include numerous sequestered proteins, including ubiquitin and chaperone proteins. Nuclear aggregates consist mainly of the toxic mHtt fragments, while cytoplasmic inclusions contain both full length and truncated mHtt. It is not entirely known if inclusion bodies merely coincide with disease, or if they themselves are cytotoxic; several lines of evidence suggest that by sequestering diffuse mHtt fragments, inclusions prolong cell survival. For example, the small molecule **B2** (Cat. No. 2855) has been shown to promote inclusion formation, whilst also preventing mHtt-mediated proteasome dysfunction in a cellular HD model. B2-induced inclusion formation also reduces α-synuclein toxicity in Parkinson's disease (PD). Greater understanding of the mechanisms behind mHtt processing and inclusion body formation may therefore help elucidate disease progression.

It has also been suggested that the presence of cellular aggregates stimulates autophagy. Conversely, inhibition of autophagy increases aggregate formation and soluble mHtt levels.

Figure 6 | Therapeutic interventions in Huntington's disease

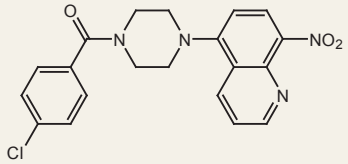


Huntingtin protein synthesis and processing is integral to HD pathology. mHtt is generated by translation of an allele containing over 35 CAG repeats. It is processed by proteolytic enzymes (namely calpains, caspases and MMPs) to generate toxic N-terminal fragments. These fragments form inclusion bodies in the cytoplasm and nucleus of the neuron, a key hallmark of HD pathology. The interactions of mHtt with a variety of cellular processes and proteins has resulted in the identification of numerous therapeutic targets; a range of small molecules acting at these targets exhibit beneficial effects in transgenic HD models. These include: antioxidants; calcium signaling inhibitors; protease inhibitors; autophagy activators; SIRT1 inhibitors; inducers of heat shock response; histone deacetylase (HDAC) inhibitors; promoters of inclusion formation; and finally, small interfering RNA (siRNA) (examples shown in green). Small molecules have also been used to generate toxin models of HD (examples shown in red). Abbreviations: 3-NP – 3-Nitropropionic acid; BDNF – brain-derived neurotrophic factor; Hsp40 – heat shock protein 40; Hsp70 – heat shock protein 70; IP_3R – IP_3 receptor; MMPs – matrix metalloproteinases; NMDAR – NMDA receptor; QA – quinolinic acid; ROS – reactive oxygen species; UPS – ubiquitin-proteasome system; VGCC – voltage-gated calcium channel.

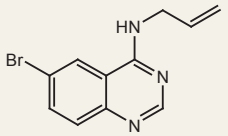
A variety of autophagy-inducing compounds have shown efficacy in HD models: **rapamycin** (Cat. No. 1292) inhibits mTOR, a negative regulator of autophagy that is also sequestered into aggregates. Rapamycin has been shown to lower Htt accumulation in cell models; it also protects against neurodegeneration in a fly model of HD. **SMER 28** (Cat. No. 4297) increases autophagosome synthesis and enhances the clearance of mHtt in mammalian cells. Additionally, the Ca^{2+} channel blocker and autophagy activator, **verapamil** (Cat. No. 0654), exhibits neuroprotective properties in various HD models. The deacetylase sirtuin 1 (SIRT1) prevents autophagic degradation of Htt by removing its acetyl tags. Selective SIRT1 inhibitors, such as **EX 527** (selisistat, Cat. No. 2780), may therefore aid Htt degradation via autophagy and increase its clearance. However, deacetylation of regulatory transcription factors by SIRT1 also promotes the expression of neuroprotective genes and brain-derived neurotrophic factor (BDNF).

Box 8: Proteolysis

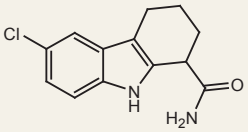
A full list of targets and related products are listed on pages 24-33



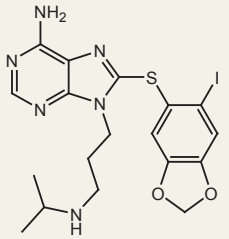
B2 (2855)
Promotes inclusion formation in cellular models of HD



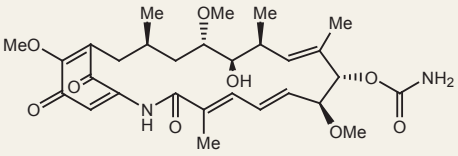
SMER 28 (4297)
Positive regulator of autophagy



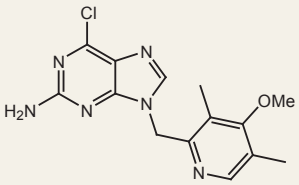
EX 527 (2780)
Selective SIRT1 inhibitor



PU H71 (3104)
Potent Hsp90 inhibitor



Geldanamycin (1368)
Selective Hsp90 inhibitor



BIIB 021 (4608)
Selective Hsp90 inhibitor

mHtt is subject to misfolding due to its abnormally long polyglutamine tract. Chaperone proteins are of interest in HD research, since they re-fold misfolded proteins and can suppress the generation of polyglutamine oligomers that later form aggregates. Chaperones are also known as heat shock proteins, of which three are of significance in HD: Hsp90, Hsp70 and Hsp40. Hsp70 and Hsp40 have been shown to attenuate the formation of fibrils by polyglutamine proteins, while Hsp90 counts Htt and mHtt amongst its client proteins. Inhibition of Hsp90 destabilizes huntingtin, aiding its clearance by the ubiquitin-proteasome system (UPS). Hsp90 inhibition, by compounds such as **geldanamycin** (Cat. No. 1368), also induces the expression of Hsp70 and Hsp40, inhibiting mHtt aggregation by activating a heat shock response. **Celastrol** (Cat. No. 3203) also induces a heat shock response and has been identified in various screens for Htt aggregation. Additional Hsp90 inhibitors, such as **PU H71** (Cat. No. 3104) and **BIIB 021** (Cat. No. 4608) may also be useful tools (Box 8).

Transcriptional Dysregulation

mHtt and its fragments can bind directly to transcription factors, altering gene expression. Intranuclear aggregates containing mHtt sequester CBP (CREB-binding protein), the protein that binds CREB (cyclic AMP response element-binding protein). mHtt binds to the acetyltransferase domain of CBP, alongside the co-activator p300. The resulting reduction in acetyltransferase activity can be countered by use of histone deacetylase (HDAC) inhibitors; **sodium butyrate** (Cat. No. 3850) improves survival, while brain-penetrant **SAHA** (Cat. No. 4652) attenuates motor deficits in HD mouse models.

Transcriptional dysregulation affects levels of **BDNF** (Cat. No. 2837) and its receptor, TrkB, both of which are often downregulated in HD. Reducing BDNF production increases neuronal loss, so restoring it to normal levels could aid the survival of striatal neurons. Increasing BDNF levels by upstream and downstream pathways may be therapeutically viable options. Infusion of recombinant BDNF, use of cell grafts releasing BDNF, and BDNF mimetics are all potential strategies currently undergoing basic research. TrkB receptors may be transactivated by adenosine A_{2A} receptors; inhibition of the latter, by compounds such as **SCH 58261** (Cat. No. 2270), is neuroprotective in excitotoxic models of HD, suggestive of a role for TrkB in excitotoxicity.

Mitochondrial Dysfunction

Neurons generally require high levels of ATP to maintain functions such as membrane polarization and vesicle trafficking. MSNs in particular require a lot of energy from oxidative phosphorylation, and so are especially sensitive to the mitochondrial dysfunction that is often evident in HD models. mHtt associates with the outer membrane of mitochondria, resulting in an impairment of the electron transport chain complexes II and III. Succinate dehydrogenase (mitochondrial complex II), can be targeted by the compounds **3-Nitropropionic acid** (3-NP, Cat. No. 4849) and **methylmalonate** (Cat. No. 4979); 3-NP generates HD disease-like pathology, while methylmalonate induces neuronal cell death. Impaired mitochondrial function has also been correlated with increased activity of the enzyme transglutaminase 2 (TG2). TG2 accumulates in cells under stress, and is upregulated in animal models of HD. Its deletion in two HD mouse models improved survival

and reduced neuronal death. Pharmacological inhibition of TG2 reverses susceptibility of human HD cells to 3-NP, and also mitigates transcriptional dysregulation. **Cystamine** (Cat. No. 4981) is a transglutaminase inhibitor that also increases BDNF secretion (and thus endogenous BDNF levels). It has been shown to improve motor performance and prolong survival in HD mice.

Mitochondria are closely linked to the production of reactive oxygen species (ROS). Excess levels of ROS result in oxidative stress, which is elevated in HD cells. Antioxidants have subsequently been the subject of HD trials; Nrf2, a transcription factor involved in the antioxidant response, and which is activated by stress, is also neuroprotective in an HD model. Nrf2 reduces the mean lifetime of polypeptides containing a polyQ expansion, and also increases neuronal survival *in vitro*. Consequently, Nrf2 is a key contributor to mHtt clearance, and activators of Nrf2, such as **TAT 14** (Cat. No. 4811), **DMF** (Cat. No. 4512) and **MMF** (Cat. No. 4511) may be useful tools.

Excitotoxicity

Glutamate

As discussed above, HD primarily affects striatal MSNs, a population of neurons that receives both glutamate signals from the cortex and dopamine signals from the substantia nigra. A long-standing hypothesis postulates that high levels of excitatory neurotransmitters and/or activation of postsynaptic glutamate receptors (in particular the NMDA receptor) on MSN membranes sensitizes them to excitotoxic cell death. The combination of numerous glutamatergic afferents and unique NMDA receptor subtype composition (NR1A and NR2B) in MSNs could make them vulnerable to injury in HD. Since MSNs are GABAergic, the loss of their inhibitory input to the globus pallidus is thought to underlie the choreic movements characteristic of HD.

mHtt is believed to enhance the activity of NMDA receptors, and NR1A and NR2B are particularly susceptible to an increase in current flow mediated by mHtt. Agonists and antagonists of NMDA receptors have been utilized widely in basic HD research. **Quinolinic acid** (Cat. No. 0225), an endogenous NMDA receptor agonist, is often used to generate HD models, while the NMDA receptor antagonist **(+)-MK-801** (Cat. No. 0924) has been shown to prevent neuronal cell loss induced by mitochondrial toxins. **Dimebon** (Cat. No. 3201) exhibits affinity for NMDA receptors, and displays neuroprotective effects in HD cellular models, but is no longer under clinical development for HD therapy (Box 9).

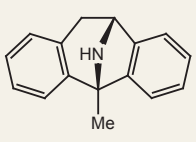
Rate of glutamate uptake has been shown to be inversely related to the number of CAG repeats; rate of glutamate uptake, and therefore clearance from the synaptic cleft, is low in HD brain tissues. The expression and function of the rodent glutamate transporter GLT-1 (ortholog of EAAT2) is decreased by mHtt. Increasing glutamate uptake or inhibiting its release may therefore be advantageous. The anticonvulsant **lamotrigine** (Cat. No. 1611) inhibits glutamate release and may slow the progression of HD. However, the glutamate release inhibitor **riluzole** (Cat. No. 0768) showed no beneficial effects in a phase III HD trial.

Dopamine

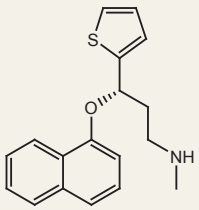
Dopamine is thought to act synergistically with glutamate to increase Ca^{2+} levels, sensitizing striatal neurons to mHtt toxicity and inducing apoptosis in MSNs. High doses of dopamine

Box 9: Excitotoxicity

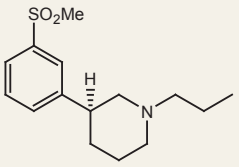
A full list of targets and related products are listed on pages 24-33



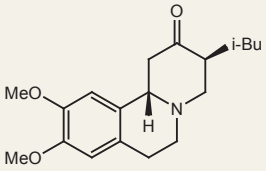
(+)-MK 801 (0924)
Non-competitive NMDA antagonist; acts at ion channel site



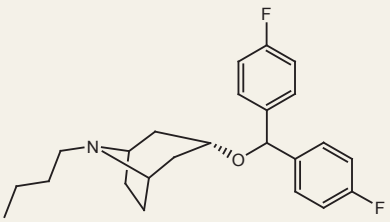
(*S*)-Duloxetine (4798)
Potent 5-HT, norepinephrine and dopamine uptake inhibitor



OSU 6162 (2599)
Dopamine stabilizer



Tetrabenazine (2175)
Potent inhibitor of vesicular monoamine transport



JHW 007 (4351)
High asffinity dopamine uptake inhibitor

Huntington's Disease – continued

can also induce cell death of striatal neurons, likely via oxidative stress. Administration of the dopamine precursor **L-DOPA** (Cat. No. 3788) consistently elevates dopamine levels and increases loss of MSNs in HD mice, as well as worsening dyskinetic symptoms in HD patients. Conversely, L-DOPA has a beneficial effect in PD patients, restoring motor function by elevating dopamine concentrations that are affected by degeneration of the substantia nigra. Motor dysfunction and MSN loss is also evident in dopamine transporter knockout mice, which have consistently high dopamine levels.

Dopamine 'stabilizers', such as pridopidine and **OSU-6162** (Cat. No. 2599), have been shown to decrease locomotor activity when dopamine levels are high, in animal models. Both bind and rapidly dissociate from dopamine D_2 receptors, which, alongside D_1 receptors, are widely expressed in MSNs. Recent research has suggested that the effects of these compounds may also be mediated by σ_1 receptors, for which they display nanomolar affinity *in vitro*. **Tetrabenazine** (Cat. No. 2175), the reversible VMAT2 inhibitor, is believed to improve motor function by depleting dopamine storage vesicles, but exhibits some serious side-effects, including depression due to lowered serotonin levels. Another VMAT2 inhibitor, **reserpine** (Cat. No. 2742), also depletes dopamine stores, but exhibits irreversible binding and is more toxic.

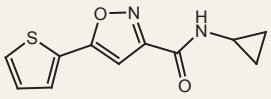
Stem Cells

Stem cells have applications in a variety of diseases, not least neurodegenerative disorders. Three major types of stem cell exist: embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and adult stem cells, the latter of which includes mesenchymal, hematopoietic and neural stem cells. With regard to HD research, iPSCs hold a great deal of interest, due to the fact that they can be derived from easily obtained somatic cells that contain the disease mutation. Consequently, they provide researchers with a source of cells for drug screening, disease modeling and cell replacement therapy, following directed differentiation into the cell type of interest (e.g. medium spiny neurons).

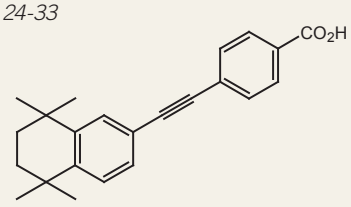
Neuronal differentiation of stem cells can be achieved with a range of small molecules (Box 10). The synthetic retinoid **EC 23** (Cat. No. 4011) and GSK-3β inhibitor **TWS 119** (Cat. No. 3835) can both induce neuronal differentiation in ESCs, while the γ-secretase inhibitor **DAPT** (Cat. No. 2634) induces neuronal differentiation from ESC-derived embryoid bodies. **SAG** (Cat. No. 4366) is a hedgehog signaling activator that induces the differentiation of dopaminergic neurons from iPSCs. Other compounds include **ISX 9** (Cat. No. 4439), which enhances NeuroD1 expression to induce cortical neuron differentiation, and **metformin** (Cat. No. 2864), which promotes neurogenesis from neural precursors. Thus, different stem and progenitor cells can be coaxed into specific cell types for regenerative therapy. Recent research has generated replacement MSNs from neural stem cells by use of BDNF and noggin proteins. Transplantation of ESC-derived GABA neurons was shown to correct motor problems in quinolinic acid-lesioned mice, while transplantation of human adipose-derived stem cells was also shown to reduce loss of striatal neurons and lower the number of Htt aggregates in a quinolinic acid-lesioned rat model.

Box 10: Stem Cells

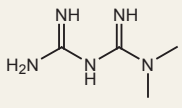
A full list of targets and related products are listed on pages 24-33



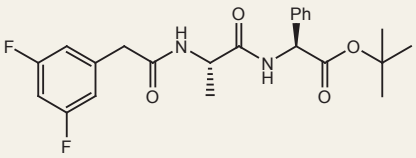
ISX 9 (4439)
Neurogenic agent; induces NeuroD1 expression



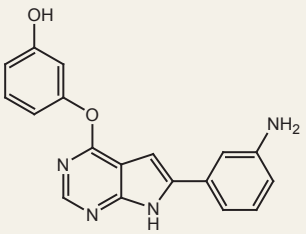
EC 23 (4011)
Synthetic retinoid; induces neural differentiation of hESCs



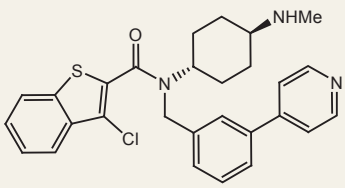
Metformin (2864)
Activator of LKB1/AMPK; enhances neurogenesis



DAPT (2634)
γ-secretase inhibitor; induces neuronal differentiation



TWS 119 (3835)
GSK-3β inhibitor; induces neuronal differentiation in ESCs



SAG (4366)
Enhances neuronal differentiation of iPSCs into dopaminergic neurons; Smo agonist

While *ex vivo* techniques (i.e. drug screening) may be readily achievable, the transplantation of modified cells into humans is subject to great scrutiny and legislation, since the safety of such therapies is not entirely known. Likewise, the function and integration of these cells would need to be assessed. Nevertheless, stem cells provide a viable alternative to animal or *in vitro* models of HD, which do not always recapitulate the disease characteristics accurately.

Additional Targets

Kynurenine monooxygenase

The enzyme kynurenine 3-monooxygenase (KMO, also known as kynurenine 3-hydroxylase) is involved in tryptophan metabolism. Metabolites in the kynurenine pathway, generated by tryptophan degradation, have been linked to HD; excitotoxicity and free radical generation are associated with low levels of kynurenic acid. The KMO inhibitor **Ro 61-8048** (Cat. No. 3254) increases levels of kynurenic acid, lowering levels of extracellular glutamate and preventing synaptic loss in a mouse model of HD. Increased concentrations of kynurenic acid also antagonize the glycine site of NMDA receptors.

ERK pathway

The antioxidants **fisetin** (Cat. No. 5016, Figure 7) and **resveratrol** (Cat. No. 1418), have been shown to improve cell survival and exhibit neuroprotective activity, respectively, in two different HD models. This activity is thought to result from the activation of ERK by these two compounds. Fisetin has also been shown to reduce neurodegeneration in flies, and increase median lifespan of flies and mice expressing mHtt.

In addition, ERK may be activated by TrkB receptors, following BDNF binding. In *Drosophila* glial cells, mHtt inhibits ERK-dependent expression of glutamate transporters, which could contribute to excitotoxicity. ERK inhibitors, such as **FR 180204** (Cat. No. 3706) and **TCS ERK 11e** (Cat. No. 4465) may therefore be useful tools for studying the role of ERK in HD pathology.

Psychiatric symptoms

Antidepressants (mainly selective serotonin reuptake inhibitors, SSRIs) and antipsychotics may also be used to counter the psychiatric manifestations of HD. SSRIs such as **citalopram** (Cat. No. 1427) increase serotonin levels by preventing its reuptake into presynaptic cells; by doing so, they raise BDNF levels. Certain SSRIs have also been shown to increase neurogenesis, motor control and cognitive ability in mouse HD models. For example, **paroxetine** (Cat. No. 2141) attenuates motor dysfunction and increases survival in HD mice; **fluoxetine** (Cat. No. 0927) has been shown to improve cognitive function in transgenic HD mice, as well as improving neurogenesis by increasing neuronal differentiation of proliferating cells. **Sertraline** (Cat. No. 2395) also promotes neurogenesis and raises BDNF levels in R6/2 transgenic mice.

Figure 7 | *Vaccinium corymbosum* – a source of fisetin

The blueberry fruit (*Vaccinium corymbosum*) is a source of the antioxidant fisetin, an ERK activator that has been shown to improve survival in cells expressing mHtt.

Future Directions

While no current treatments stop or reverse the progression of HD, it is hoped that the discovery and/or elucidation of potential drug targets may help drive the development of disease-modifying therapies. In spite of similar neurodegenerative mechanisms, HD differs from AD and PD by virtue of the fact that it is a purely genetic disorder. As a result of this, gene silencing is undergoing research in HD mouse models, with small interfering RNAs (siRNAs) and antisense oligonucleotides being used to selectively target the messenger RNA (mRNA) encoded by the mutant allele. Clinical trials in HD patients using this approach are on the horizon. As with other neurodegenerative diseases, stem cells may also be of future benefit; they can be coaxed into specific cell types for regenerative therapy, ideally replacing the lost neurons and restoring normal brain function. Fundamental questions regarding the roles of Htt and its interactions with intracellular proteins have yet to be answered, but it is hoped that research into Huntington's disease may help inform research into other neurodegenerative disorders with similar pathologies.

List of Acronyms

Acronym	Definition
3-NP	3-Nitropropionic acid
5-HT	5-hydroxytryptamine; serotonin
6-OHDA	6-hydroxydopamine
ACh	Acetylcholine
AD	Alzheimer's disease
Akt	Protein kinase B
APP	Amyloid precursor protein
ASK1	Apoptosis signal-regulating kinase 1
ATP	Adenosine-5′-triphosphate
Aβ	Amyloid-β
BACE-1	β-secretase
BDNF	Brain-derived neurotrophic factor
cAMP	Cyclic AMP
CB	Cannabinoid
CBP	CREB-binding protein
Cdk5	Cyclin dependent kinase 5
ChAT	Choline acetyltransferase
CK	Casein kinase
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CREB	cAMP response element-binding protein
DDC	Dopa decarboxylase
DR	Dorsal raphe nucleus
Dyrk	Dual-specificity tyrosinephosphorylation-regulated kinase
EGCG	Epigallocatechin gallate
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GPe	External globus pallidus
GPi	Internal globus pallidus
GRK2	G protein-coupled receptor kinase 2
GSK-3	Glycogen synthase kinase-3
HD	Huntington's disease
Hsp40	Heat shock protein 40 (DNAJ)
Hsp70	Heat shock protein 70

Acronym	Definition
Htt	Huntingtin protein
KMO	Kynurenine 3-monooxygenase (kynurenine 3-hydroxylase)
LID	L-DOPA-induced dyskinesias
MAO-B	Monoamine oxidase B
MARK	Microtubule affinity-regulating kinase
mHtt	Mutant huntingtin protein
MMP	Matrix metalloproteinase
MMT	Methylcyclopentadienyl manganese tricarbonyl
MPP^+	1-methyl-4-phenyl-pyridium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mPTP	Mitochondrial permeability transition pore
mRNA	Messenger RNA
MSN	Medium spiny neuron
NMDA	N-methyl-D-aspartate
NMDAR	NMDA receptor
PD	Parkinson's disease
PI 3-K	Phosphoinositide 3-kinase
PKA	Cyclic AMP-dependent protein kinase
PKC	Protein kinase C
PolyQ	Polyglutamine
ptau	Hyperphosphorylated tau
QA	Quinolinic acid
RAR	Retinoic acid receptor
RNA	Ribonucleic acid
ROS	Reactive oxygen species
siRNA	Small interfering RNA
SIRT1	Sirtuin 1
SNpc	Substantia nigra pars compacta
SSRI	Selective serotonin reuptake inhibitor
TG2	Transglutaminase 2
UPS	Ubiquitin-proteasome system
VGCC	Voltage-gated calcium channel
VMAT	Vesicular monoamine transporter
wt	Wild-type

Neurodegeneration Research Products from Tocris

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
5-HT Receptors					
Agonists	0529	8-Hydroxy-DPAT	Selective 5-HT_{1A} agonist; also has moderate affinity for 5-HT_7	10 mg 50 mg	69 249
	1771	S 14506	Highly potent 5-HT_{1A} agonist; displays unique binding mechanism	10 mg 50 mg	185 779
	2854	Tandospirone	Selective 5-HT_{1A} partial agonist	10 mg 50 mg	139 585
	2491	Xaliproden	High affinity 5-HT_{1A} agonist; orally active	10 mg 50 mg	145 609
Antagonists	3326	BGC 20-761	High affinity 5-HT_6 antagonist	10 mg 50 mg	165 695
	1322	GR 113808	Potent and selective 5-HT_4 antagonist	10 mg 50 mg	169 715
	1658	GR 125487	Potent and selective 5-HT_4 antagonist; active *in vivo*	10 mg 50 mg	185 779
	4964	R 1485	Selective and high affinity 5-HT_6 antagonist	10 mg 50 mg	195 819
	3189	SB 399885	Potent and selective 5-HT_6 antagonist	10 mg 50 mg	195 819
Acetylcholine Nicotinic Receptors					
Agonists	4234	4BP-TQS	Allosteric agonist at α7 nAChR	10 mg	185
	4341	A 582941	Partial agonist at α7 nAChR	10 mg 50 mg	195 819
	5017	A 85380	High affinity and selective α4β2 agonist	10 mg	189
	5236	CC4	High affinity and subtype-selective α6β2 and α4β2 partial agonist	10 mg 50 mg	149 629
	4557	GTS 21	Partial agonist at α7 nAChR	10 mg 50 mg	185 779
	3546	(-)-Nicotine	Prototypical nAChR agonist	50 mg	65
	4831	NS 3861	α3β2 full agonist; also α3β4 partial agonist	10 mg 50 mg	139 585
	1053	RJR 2403	α4β2 selective nicotinic agonist	10 mg 50 mg	129 545
	3855	RuBi-Nicotine	Caged nicotine; rapidly excitable by visible light	10 mg	425
	4766	SIB 1508Y	Potent agonist of α4β2, α2β4, α4β4 and α3β4 nACh receptors	10 mg 50 mg	185 779
	4764	SIB 1553A	Subunit selective nAChR agonist	10 mg 50 mg	159 669
Antagonists	2133	α-Bungarotoxin	α7 subtype-selective nAChR antagonist	1 mg	169
	3119	α-Conotoxin ImI	α7 and α9 selective nAChR antagonist	500 µg	235
	2349	Dihydro-β-erythroidine	Selective α4 nAChR antagonist	10 mg 50 mg	175 735
	4424	SR 16584	Selective α3β4 nAChR antagonist	10 mg 50 mg	195 819
Modulators	4571	A 867744	Positive allosteric modulator of α7 nAChR	10 mg 50 mg	179 755
	5112	NS 9283	Positive allosteric modulator of α4β2	10 mg 50 mg	175 735
Adenosine A_{2A} Receptors					
Agonists	1063	CGS 21680	A_{2A} agonist	10 mg 50 mg	265 1115
	4603	LUF 5834	Potent adenosine A_{2A} and A_{2B} receptor partial agonist	10 mg 50 mg	195 819
	4334	PSB 0777	Potent adenosine A_{2A} agonist	10 mg 50 mg	209 879

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
Antagonists	3306	8-(3-Chlorostyryl)caffeine	Selective A_{2A} antagonist; also MAO-B inhibitor	10 mg 50 mg	89 365
	5147	Istradefylline	Potent and selective adenosine A_{2A} receptor antagonist	10 mg 50 mg	155 655
	4783	Lu AA 47070	Prodrug of a potent and selective adenosine A_{2A} receptor antagonist	10 mg 50 mg	195 819
	2270	SCH 58261	Potent, highly selective A_{2A} antagonist	10 mg 50 mg	185 779
	4407	TC-G 1004	Potent and selective A_{2A} antagonist	10 mg 50 mg	209 879
	1036	ZM 241385	Potent, highly selective A_{2A} antagonist	10 mg 50 mg	155 655
Amyloid β Peptides					
Inhibitors	4924	CEP 1347	Blocks Aβ-induced cortical neuron apoptosis	1 mg	239
	3360	CGP 52411	Inhibits Aβ42 fibril formation; also EGFR inhibitor	10 mg 50 mg	145 609
	2442	CGP 53353	Inhibitor of *de novo* Aβ42 assembly; PKCβII inhibitor	10 mg	229
	4524	EGCG	Inhibits formation of amyloid fibrils	50 mg	59
	2408	Ro 90-7501	Inhibitor of Aβ42 fibril formation	10 mg 50 mg	155 655
	4699	SEN 1269	Amyloid-β aggregation inhibitor	10 mg 50 mg	189 795
Other	5053	AC 186	Decreases Aβ levels in combination with ACP-105; ERβ agonist	10 mg 50 mg	199 839
	1191	Amyloid β-Peptide (1-40) (human)	Amyloid β-protein fragment	1 mg	399
	2424	Amyloid β-peptide (1-40) (rat)	Amyloid β-protein fragment	1 mg	205
	1428	Amyloid β-Peptide (1-42) (human)	Predominant amyloid β-protein fragment	100 µg	139
	2425	Amyloid β-peptide (1-42) (rat)	Predominant amyloid β-protein fragment	500 µg	339
	3945	Colivelin	Neuroprotective peptide; protects against β-amyloid neurotoxicity	500 µg	265
	4803	CRANAD 2	Near-infrared probe that detects Aβ40 aggregates	10 mg	249
	5081	J 147	Neuroprotective and neurotrophic compound; reduces Aβ40 and Aβ42 levels	10 mg 50 mg	155 655
	3144	K 114	Amyloid fibril-specific fluorescent dye	10 mg 50 mg	109 459
	4920	Methoxy-X04	Fluorescent amyloid β detector; brain penetrant	10 mg 50 mg	149 629
Antidepressants and SSRIs					
	4456	Amitriptyline	5-HT and noradrenaline re-uptake inhibitor	50 mg	59
	1427	Citalopram	Highly potent and selective 5-HT uptake inhibitor	10 mg 50 mg	139 585
	0927	Fluoxetine	5-HT re-uptake inhibitor	10 mg 50 mg	89 375
	1033	Fluvoxamine	5-HT re-uptake inhibitor	10 mg 50 mg	89 375
	2141	Paroxetine	Highly potent and selective 5-HT uptake inhibitor	10 mg 50 mg	125 525
	2395	Sertraline	5-HT re-uptake inhibitor	10 mg 50 mg	155 655
	2917	Venlafaxine	Dual 5-HT/noradrenaline re-uptake inhibitor	10 mg 50 mg	115 449
Antioxidants					
	4055	L-Ascorbic acid	Naturally occurring antioxidant	50 mg	45
	3203	Celastrol	Antioxidant and anti-inflammatory agent	10 mg 50 mg	179 755

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
	3003	Coenzyme Q10	Antioxidant	10 mg 50 mg	75 315
	2841	Curcumin	Antitumor, anti-inflammatory and antioxidant	50 mg	65
	5245	Ebselen	Glutathione peroxidase mimic; peroxynitrite scavenger	10 mg 50 mg	75 315
	5016	Fisetin	Naturally occuring flavonoid and antioxidant; neuroprotective	50 mg	59
	5219	L-Glutathione Reduced	Endogenous antioxidant	5 g	39
	3550	Melatonin	Powerful antioxidant *in vivo*; endogenous hormone	50 mg	65
	1418	Resveratrol	Phytoestrogen with antioxidant effects	100 mg	105
	2302	Sanguinarine	Inhibitor of protein phosphatase 2C (PP2C); exhibits antioxidant and anti-inflammatory activity	10 mg 50 mg	145 609
Atypical Antipsychotics					
	0444	Clozapine	Dopamine receptor and 5-$HT_{2A/2C}$ antagonist; atypical antipsychotic	50 mg 500 mg	135 669
	4349	Olanzapine	5-HT_{2A}/D_2 antagonist; atypical antipsychotic	10 mg 50 mg	69 275
	4735	Quetiapine	5-HT_2/D_2 antagonist; atypical antipsychotic	50 mg	109
	2865	Risperidone	5-HT_{2A} antagonist; atypical antipsychotic	10 mg 50 mg	139 585
	3085	Ziprasidone	5-HT_{2A}/D_2 antagonist; atypical antipsychotic	10 mg 50 mg	139 585
Autophagy					
Activators	0681	L-690,330	Inositol monophosphatase inhibitor; induces autophagy independently of mTOR inhibition	10 mg 50 mg	155 655
	1292	Rapamycin	mTOR inhibitor; induces autophagy	1 mg	255
	4297	SMER 28	Positive regulator of autophagy	10 mg 50 mg	109 459
Inhibitors	3977	3-Methyladenine	Class III PI 3-kinase inhibitor; inhibits autophagy	50 mg	105
Bax					
Activators	4810	BAM 7	Selective Bax activator; induces Bax-mediated apoptosis	10 mg 50 mg	185 779
	5314	SMBA 1	High affinity and selective activator of Bax	10 mg 50 mg	179 755
Inhibitors	2160	Bax channel blocker	Inhibits Bax-mediated mitochondrial cytochrome c release	10 mg 50 mg	169 715
	1785	Bax inhibitor peptide V5	Inhibitor of Bax-mediated apoptosis	1 mg	169
	3794	iMAC2	Inhibitor of Bid-induced Bax activation	10 mg 50 mg	199 839
Calcium Channels					
Activators	1544	(±)-Bay K 8644	Ca^{2+} channel activator (L-type)	10 mg 50 mg	165 695
Blockers	0685	Diltiazem	Ca^{2+} channel blocker (L-type)	1 g	95
	2004	Isradipine	Ca^{2+} channel blocker (L-type)	10 mg 50 mg	129 545
	0654	Verapamil	Ca^{2+} channel blocker (L-type)	1 g	95
Cannabinoid Receptors					
Agonists	1319	ACEA	Potent, highly selective CB_1 agonist	5 mg 25 mg	69 295
	3500	(±)-CP 47497	Potent CB_1 agonist	10 mg 50 mg	139 585
	0966	HU 210	Highly potent cannabinoid receptor agonist	5 mg 25 mg	185 779
	1343	JWH 133	Potent, selective CB_2 agonist	10 mg	245

Neurodegeneration Research Products – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
	1038	WIN 55,212-2	Highly potent cannabinoid receptor agonist	10 mg 50 mg	89 375
Antagonists	5443	AM 6545	High affinity and selective CB1 antagonist	10 mg 50 mg	195 819
	4756	COR 170	Selective CB_2 receptor inverse agonist	10 mg 50 mg	189 795
Modulators	5321	PSNCBAM-1	CB_1 receptor negative allosteric modulator	10 mg 50 mg	179 755
Casein Kinases					
Inhibitors	5329	CKI 7	CK1 inhibitor	10 mg 50 mg	179 755
	2902	D 4476	Selective CK1 inhibitor; also inhibits TGF-βRI	10 mg 50 mg	195 819
	3610	(*R*)-DRF053	Dual cdk/CK1 inhibitor	10 mg 50 mg	235 989
	3316	PF 670462	Potent and selective CK1ε and CK1δ inhibitor	10 mg 50 mg	195 819
	2275	TBB	Selective cell-permeable CK2 inhibitor	10 mg 50 mg	89 339
	4432	TTP 22	High affinity, selective CK2 inhibitor	10 mg 50 mg	169 715
Catechol *O*-Methyltransferase (COMT)					
Inhibitors	4720	Entacapone	Potent COMT inhibitor; blocks α-synuclein aggregation	10 mg 50 mg	59 249
	0483	OR-486	COMT inhibitor	50 mg	129
Cholinesterases					
Inhibitors	0388	Ambenonium	Cholinesterase inhibitor	10 mg 50 mg	129 545
	4385	Donepezil	Potent AChE inhibitor	10 mg 50 mg	75 299
	0686	Galanthamine	Cholinesterase inhibitor	100 mg	139
	0622	Physostigmine	Cholinesterase inhibitor	100 mg	59
	4440	Rivastigmine	Dual AChE and BChE inhibitor	50 mg	135
	0965	Tacrine	Cholinesterase inhibitor	100 mg	65
Cyclin-dependent Kinases					
Inhibitors	5608	BS 181	Selective cdk7 inhibitor	10 mg 50 mg	175 735
	3605	(*R*)-CR8	Dual cdk1/cdk5 inhibitor; also inhibits CK1	10 mg 50 mg	229 965
	3094	Flavopiridol	Cdk inhibitor	10 mg 50 mg	185 779
	4786	PD 0332991	Potent, selective cdk4/6 inhibitor; brain penetrant	10 mg 50 mg	219 925
	1581	Purvalanol B	Cdk inhibitor	10 mg 50 mg	205 865
	4181	Ro 3306	Cdk1 inhibitor	10 mg 50 mg	195 819
	4875	Senexin A	Cdk8 inhibitor	10 mg	205
Deacetylases					
Inhibitors	4754	AK 7	Selective SIRT2 inhibitor; brain penetrant	10 mg 50 mg	139 585
	2780	EX 527	Selective SIRT1 inhibitor	1 mg 10 mg 50 mg	89 185 749

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
	4830	LMK 235	Selective HDAC4/HDAC5 inhibitor	10 mg 50 mg	149 629
	4077	MC 1568	Selective HDAC class II (IIa) inhibitor	10 mg 50 mg	185 779
	4652	SAHA	Class I and II HDAC inhibitor	10 mg 50 mg	69 229
	5457	SirReal 2	Selective inhibitor of SIRT2	10 mg 50 mg	189 795
	2682	Sodium 4-Phenylbutyrate	HDAC inhibitor	100 mg	95
	3850	Sodium butyrate	HDAC inhibitor	50 mg	59
	4270	TC-H 106	Class I HDAC inhibitor	10 mg 50 mg	169 715
	3402	Tubacin	HDAC6 inhibitor; inhibits α-tubulin deacetylation	1 mg	265
Decarboxylases					
Inhibitors	0455	(*S*)-(-)-Carbidopa	Aromatic L-amino acid decarboxylase inhibitor	25 mg	95
	0584	L-(-)-α-Methyldopa	Aromatic L-amino acid decarboxylase inhibitor	1 g	95
Dopamine Metabolism					
	3788	L-DOPA	Dopamine precursor	50 mg	59
	2599	OSU 6162	Dopamine stabilizer	10 mg 50 mg	155 655
Dopamine Receptors					
Agonists	2073	(*R*)-(-)-Apomorphine	Dopamine receptor agonist	50 mg	95
	2759	B-HT 920	D_2 receptor agonist; also α2 agonist and 5-HT_3 antagonist	10 mg 50 mg	129 545
	0427	Bromocriptine	Selective D_2-like agonist	50 mg	115
	2664	Cabergoline	Selective D_2-like agonist	10 mg 50 mg	195 819
	3992	NPEC-caged-dopamine	Caged dopamine	10 mg	179
	1031	Piribedil	Dopamine receptor agonist	10 mg 50 mg	125 525
	4174	Pramipexole	Selective D_3 agonist	10 mg 50 mg	155 655
	1061	(-)-Quinpirole	Selective D_2-like agonist	10 mg 50 mg	129 545
	3680	Ropinirole	Selective D_2-like agonist	10 mg 50 mg	75 315
	3896	Rotigotine	Dopamine D_2/D_3 agonist	10 mg 50 mg	119 495
	4932	RuBi-Dopa	Caged dopamine; exhibits two-photon sensitivity	10 mg	249
	1447	SKF 81297	D_1 agonist	10 mg 50 mg	195 819
Antagonists	0925	SCH 23390	Standard selective D_1-like antagonist; also 5-HT_{2C} agonist	10 mg 50 mg	139 585
Dopamine Transporters					
Inhibitors	0421	GBR 12909	Selective dopamine uptake inhibitor; also σ ligand	10 mg 50 mg	85 359
	4351	JHW 007	High affinity dopamine uptake inhibitor	10 mg 50 mg	169 715
DYRK					
Inhibitors	5075	Harmine	Potent and selective DYRK1A inhibitor	50 mg	59
	4997	INDY	DYRK1A/B inhibitor	10 mg	159
	4998	ProINDY	DYRK1A/B inhibitor; prodrug of INDY (Cat. No. 4997)	10 mg	169
	5088	TC-S 7004	Potent and selective DYRK1A/B inhibitor	10 mg 50 mg	189 795

Neurodegeneration Research Products – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
ERK					
Inhibitors	4842	BIX 02189	Selective MEK5 and ERK5 inhibitor	10 mg 50 mg	195 819
	5393	ERK5-IN-1	Potent and selective ERK5 inhibitor	10 mg 50 mg	239 1005
	3706	FR 180204	Selective ERK inhibitor	10 mg 50 mg	245 1029
	4465	TCS ERK 11e	Potent and selective ERK2 inhibitor	10 mg	249
Glutamate Transport					
Agonists	2277	MNI-caged-D-aspartate	Caged D-aspartate; EAAT substrate	10 mg 50 mg	205 865
Inhibitors	3697	7-Chlorokynurenic acid sodium salt	Potent competitive inhibitor of L-glutamate uptake; sodium salt of 7-Chlorokynurenic acid (Cat. No. 0237)	10 mg 50 mg	89 375
	0111	Dihydrokainic acid	EAAT2 (GLT-1)-selective non-transportable inhibitor of L-glutamate and L-aspartate uptake	1 mg 10 mg 50 mg	79 165 695
	1223	DL-TBOA	Selective non-transportable inhibitor of EAATs	10 mg 50 mg	199 839
	1611	Lamotrigine	Glutamate release inhibitor; anticonvulsant	10 mg 50 mg	139 585
	0768	Riluzole	Glutamate release inhibitor/GABA uptake inhibitor	25 mg	95
	2652	WAY 213613	Potent, non-substrate EAAT2 inhibitor	10 mg 50 mg	195 819
Other	5082	LDN 212320	Increases EAAT2 expression; neuroprotective	10 mg 50 mg	125 525
Glycogen Synthase Kinase					
Inhibitors	4431	A 1070722	Highly potent, selective GSK-3 inhibitor	10 mg 50 mg	179 755
	3966	AR-A 014418	Selective GSK-3 inhibitor	10 mg 50 mg	165 695
	3194	BIO	Potent, selective GSK-3 inhibitor	10 mg 50 mg	155 655
	3874	BIO-acetoxime	Selective GSK-3α/β inhibitor	1 mg 10 mg	129 275
	4423	CHIR 99021	Highly selective GSK-3 inhibitor	10 mg 50 mg	209 879
	4953	CHIR 99021 trihydrochloride	Hydrochloride salt of CHIR 99021 (Cat. No. 4423); selective GSK-3 inhibitor	10 mg 50 mg	229 965
	1398	Kenpaullone	GSK-3 inhibitor; also inhibits cdk	10 mg	169
	4740	Lithium carbonate	Inhibits GSK-3 *in vivo*; also Na^+/K^+ ATPase pump inhibitor	50 mg	49
	3873	MeBIO	Inactive analog of BIO (Cat. No. 3194)	10 mg	149
	1616	SB 216763	Potent, selective GSK-3 inhibitor	1 mg 10 mg 50 mg	79 169 715
	1617	SB 415286	Potent, selective GSK-3 inhibitor	10 mg 50 mg	179 745
	4353	TC-G 24	Potent and selective GSK-3β inhibitor	10 mg 50 mg	185 779
	3869	TCS 2002	Potent GSK-3β inhibitor	10 mg 50 mg	185 779
	4221	TCS 21311	GSK-3β inhibitor; also inhibits PKC and JAK3	10 mg 50 mg	229 965
GRK2					
Inhibitors	3594	GRK2i	GRK2 inhibitory polypeptide; Gβγ antagonist	1 mg	219

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
Heat Shock Proteins					
Inhibitors	1515	17-AAG	Selective Hsp90 inhibitor	1 mg	159
	4608	BIIB 021	Selective Hsp90 inhibitor	10 mg 50 mg	195 819
	4701	EC 144	High affinity, potent and selective Hsp90 inhibitor	10 mg	229
	3387	Gedunin	Hsp90 inhibitor; exhibits anticancer and antimalarial activity	10 mg	219
	1368	Geldanamycin	Selective Hsp90 inhibitor	1 mg	345
	3104	PU H71	Potent Hsp90 inhibitor	10 mg	219
	3803	VER 155008	Hsp70 inhibitor	10 mg 50 mg	195 819
Other	4734	TRC 051384	Inducer of Hsp70	10 mg	239
Hydroxylases					
Inhibitors	3254	Ro 61-8048	Potent kynurenine 3-hydroxylase inhibitor	10 mg 50 mg	165 695
LRRK2					
Inhibitors	4534	CZC 54252	Potent LRRK2 inhibitor; neuroprotective	10 mg 50 mg	205 865
	4629	GSK2578215A	Potent and selective LRRK2 inhibitor; brain penetrant	10 mg 50 mg	219 925
	4273	LRRK2-IN-1	Potent and selective LRRK2 inhibitor	10 mg 50 mg	249 1049
Microtubules					
	1364	Colchicine	Inhibitor of tubulin	1 g	115
	4056	Docetaxel	Microtubule stabilizer	10 mg 50 mg	129 545
	3502	Epothilone B	Microtubule stabilization agent; promotes tubulin polymerization	100 µg	305
	2226	Flutax 1	Fluorescent taxol derivative; binds to taxol microtubule binding site	1 mg	205
	3728	Indibulin	Microtubule destabilizer	10 mg 50 mg	155 655
	5231	MPC 6827	Inhibitor of microtubule polymerization; antimitotic and antitumor	10 mg 50 mg	185 779
	1228	Nocodazole	Microtubule inhibitor	10 mg	95
	1097	Taxol	Promotes assembly and inhibits disassembly of microtubules	10 mg 50 mg	125 475
	1256	Vinblastine	Disrupts microtubules	10 mg 50 mg	109 459
	3401	Vinorelbine	Selective mitotic microtubule antagonist	10 mg 50 mg	139 585
Monoamine Oxidase B					
Inhibitors	1095	(*R*)-(-)-Deprenyl	MAO-B inhibitor	1 g	165
	2460	Lazabemide	Selective MAO-B inhibitor	10 mg 50 mg	115 485
	4308	Rasagiline	Selective, irreversible MAO-B inhibitor	50 mg	59
Neuronal Metabolism					
	2855	B2	Promotes inclusion formation in cellular models of Huntington's and Parkinson's disease	10 mg 50 mg	139 585
	3201	Dimebon	Neuroprotectant; protects against β-amyloid neurotoxicity	1 mg 10 mg	105 219
	5131	NAB 2	Protects against α-synuclein toxicity	10 mg 50 mg	179 755
	4926	UPF 648	Potent kynurenine 3-monooxygenase (KMO) inhibitor	10 mg	285

Neurodegeneration Research Products – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
NMDA Receptors					
Agonists	3406	GLYX 13	NMDA receptor partial agonist; acts at the glycine site	1 mg	129
	2224	MNI-caged-NMDA	Caged NMDA	10 mg	255
	0225	Quinolinic acid	Endogenous NMDA agonist and transmitter candidate	1 g	75
Antagonists	4492	Cerestat	Potent and noncompetitive NMDA receptor antagonist	10 mg 50 mg	149 629
	2456	Co 101244	Highly selective NR2B antagonist	10 mg 50 mg	165 695
	0106	D-AP5	Potent, selective NMDA antagonist; more active form of DL-AP5 (Cat. No. 0105)	1 mg 10 mg 50 mg 100 mg	69 149 629 865
	4491	DQP 1105	Selective NR2C/NR2D receptor antagonist	10 mg 50 mg	169 685
	0545	Ifenprodil	Non-competitive NMDA antagonist; also σ ligand	10 mg 50 mg	89 339
	0773	Memantine	NMDA antagonist; acts at ion channel site	50 mg	105
	0924	(+)-MK 801	Non-competitive NMDA antagonist; acts at ion channel site	10 mg 50 mg	89 339
	2274	PPPA	Competitive NR2A antagonist	10 mg 50 mg	195 819
	4801	QNZ 46	NR2C/NR2D-selective NMDA receptor non-competitive antagonist	10 mg 50 mg	169 715
	2005	Ro 04-559	Selective NR2B antagonist	10 mg 50 mg	169 715
	1594	Ro 25-698	Subtype-selective NR2B antagonist	1 mg 10 mg 50 mg	79 165 695
	4163	TCN 213	Selective NR2A antagonist	10 mg 50 mg	189 795
	4072	TCN 237	Highly potent and selective NR2B antagonist	10 mg	159
Other	5376	Pregnenolone sulfate sodium salt	NMDA Potentiator	50 mg	49
Nrf2					
Activators	5145	AI-3	ARE activator; induces Nrf2-ARE-dependent transcription	10 mg 50 mg	175 735
	4737	CDDO Im	Nrf2 signaling activator	10 mg	199
	4512	DMF	Nrf2 pathway activator; neuroprotective	50 mg	49
	5293	NK 252	Nrf2 activator	10 mg 50 mg	129 545
	4511	MMF	Nrf2 pathway activator; primary metabolite of DMF (Cat. No. 4512)	50 mg	49
	5294	Oltipraz	Nrf2 activator	10 mg 50 mg	79 335
	4811	TAT 14	Nrf2 pathway activator; blocks Nrf2/Keap1 interaction	1 mg	159
Oxidative Phosphorylation					
	2966	CGP 3466B	GAPDH inhibitor; neuroprotective	10 mg 50 mg	125 495
	4979	Methylmalonate	Succinate dehydrogenase inhibitor	50 mg	49
	4849	3-Nitropropionic acid	Irreversible mitochondrial respiratory complex II inhibitor	50 mg	49
	3616	Rotenone	Inhibits complex I of the mitochondrial electron transport chain	50 mg	59

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
Poly(ADP-ribose) Polymerase					
Inhibitors	2496	DR 2313	PARP-1 and PARP-2 inhibitor	1 mg 10 mg 50 mg	69 145 609
	3255	PJ 34	Potent PARP inhibitor	10 mg 50 mg	165 695
Proteases					
Inhibitors	0448	Calpeptin	Calpain and cathepsin L inhibitor	10 mg 50 mg	145 609
	4090	Doxycycline hyclate	Broad-spectrum MMP inhibitor; tetracycline derivative	50 mg	49
	5208	E 64	Potent and irreversible cysteine protease inhibitor	10 mg 50 mg	145 609
	3995	GI 254023X	Selective ADAM10 metalloprotease inhibitor	1 mg	159
	2983	GM 6001	Broad spectrum MMP inhibitor	10 mg	275
	3268	Minocycline	MMP inhibitor; displays neuroprotective effects	50 mg	95
	2166	Z-DEVD-FMK	Cell-permeable, irreversible caspase-3 inhibitor	1 mg	295
	2163	Z-VAD-FMK	Cell-permeable, irreversible caspase inhibitor	1 mg	219
Proteasome					
Inhibitors	2564	AM 114	20S proteasome inhibitor	10 mg 50 mg	139 585
	2267	Lactacystin	Potent and selective proteasome inhibitor; cell permeable	200 µg	285
	1748	MG 132	Proteasome and calpain inhibitor; inhibits NF-κB activation	5 mg	129
	4045	PSI	Proteasome inhibitor; also prevents activation of NF-κB	5 mg	195
Protein *O*-GlcNAcase					
Inhibitors	4390	Thiamet G	Potent O-GlcNAcase inhibitor	10 mg	229
Protein Ser/Thr Phosphatase					
Activators	0744	Ceramide	Ser/Thr protein phosphatase activator	10 mg 50 mg	139 585
Inhibitors	1336	Calyculin A	Protein phosphatase 1 and 2A inhibitor	100 µg	445
	1136	Okadaic acid	Protein phosphatase 1 and 2A inhibitor	25 µg	115
Retinoic Acid Receptors					
Agonists	0760	AM 580	Retinoic acid analog; RARα agonist	10 mg 50 mg	149 629
	3824	CD 2314	Selective RARβ agonist	10 mg 50 mg	199 839
γ-Secretase					
Inhibitors	4283	Begacestat	γ-secretase inhibitor; lowers Aβ40 and Aβ42 levels	10 mg 50 mg	185 779
	2870	BMS 299897	Potent γ-secretase inhibitor	10 mg	199
	2634	DAPT	γ-secretase inhibitor	10 mg 50 mg	195 819
	4489	DBZ	γ-secretase inhibitor; inhibits Notch pathway	10 mg 50 mg	219 925
	2677	JLK 6	Inhibitor of γ-secretase-mediated βAPP processing	10 mg 50 mg	145 609
	2627	L-685,458	Potent and selective γ-secretase inhibitor	1 mg	255
	4000	MRK 560	γ-secretase inhibitor; attenuates amyloid plaque deposition	10 mg 50 mg	205 865
Stem Cells					
	2634	DAPT	γ-secretase inhibitor; induces neuronal differentiation	10 mg 50 mg	195 819
	4126	DMH-1	ALK2 inhibitor; promotes iPSC neurogenesis in combination with SB 431542 (Cat. No. 1614)	10 mg 50 mg	189 795

Neurodegeneration Research Products – continued

Class	Cat. No.	Product Name	Primary Action	Unit Size	USD
	4011	EC 23	Synthetic retinoid; induces neural differentiation of hESCs	10 mg 50 mg	155 655
	3853	ID 8	Sustains self-renewal and pluripotency of ESCs	10 mg 50 mg	169 715
	5513	Isotretinoin	Inducer of neuronal differentiation; endogenous agonist for retinoic acid receptors	50 mg	59
	4439	ISX 9	Neurogenic agent; induces neuronal differentiation of SVZ progenitors	10 mg 50 mg	169 715
	4888	KHS 101	Selective inducer of neuronal differentiation in hippocampal neural progenitors	10 mg 50 mg	149 629
	2864	Metformin	Activator of LKB1/AMPK; enhances neurogenesis	100 mg	75
	3656	Neurodazine	Induces neurogenesis in mature skeletal muscle cells	10 mg 50 mg	155 655
	3854	1-Oleoyl lysophosphatidic acid sodium salt	LPA_1 and LPA_2 agonist; inhibits differentiation of neural stem cells into neurons	1 mg	59
	0238	*O*-Phospho-L-serine	Group III mGlu agonist; enhances neuronal differentiation of progenitor cells	100 mg	75
	4076	P7C3	Neuroprotective compound; enhances neurogenesis *in vivo*	10 mg 50 mg	185 779
	4847	PluriSIn 1	Inhibitor of SCD1; selectively eliminates undifferentiated hPSCs from culture	10 mg 50 mg	105 445
	4366	SAG	Enhances neuronal differentiation of iPSCs into dopaminergic neurons; Smo agonist	1 mg	149
	3877	TCS 2210	Inducer of neuronal differentiation in MSCs	10 mg 50 mg	189 795
	3835	TWS 119	GSK-3β inhibitor; induces neuronal differentiation in ESCs	10 mg	205
	3115	WHI-P 154	JAK3 kinase inhibitor; induces differentiation of neural progenitor cells	10 mg 50 mg	155 655
Tau Aggregation					
	1467	Daunorubicin	RNA synthesis inhibitor	10 mg	139
	2252	Doxorubicin	DNA topoisomerase II inhibitor; reduces intracellular tau levels	10 mg 50 mg	139 585
	3213	Methylene Blue	Biological stain; inhibits tau filament formation	50 mg	75
Transglutaminase					
Inhibitors	4981	Cystamine	Transglutaminase inhibitor; neuroprotective	50 mg	49
	4602	LDN 27219	Transglutaminase 2 (TG2) inhibitor; reversible	10 mg 50 mg	169 715
Trk Receptors					
Agonist	2837	BDNF (human)	Activates TrkB and p75 receptors	10 µg	325
Other	5046	LM11A 31	Nonpeptide $p75^{NTR}$ ligand; neuroprotective	10 mg 50 mg	105 445
	5101	PD 90780	Inhibits NGF binding to $p75^{NTR}$	10 mg 50 mg	189 795
Vesicular Monoamine Transporters (VMATs)					
Inhibitors	2742	Reserpine	Inhibitor of vesicular monoamine transport	1 g	125
	5168	Rose Bengal	Potent VGlut and VMAT inhibitor; cell permeable	50 mg	39
	2175	Tetrabenazine	Potent inhibitor of vesicular monoamine transport	10 mg 50 mg	135 559
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Further Reading

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

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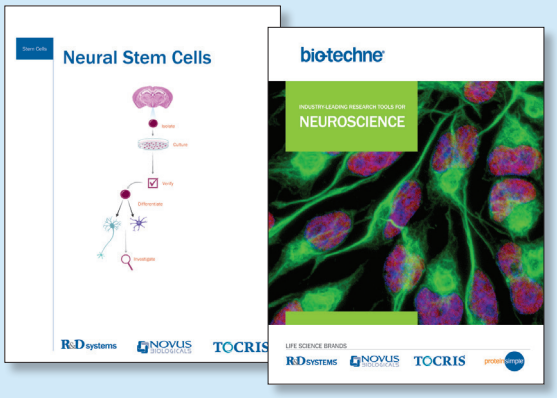

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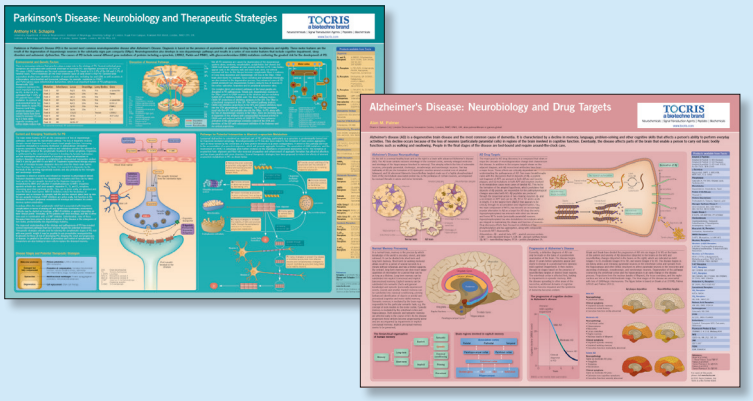

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