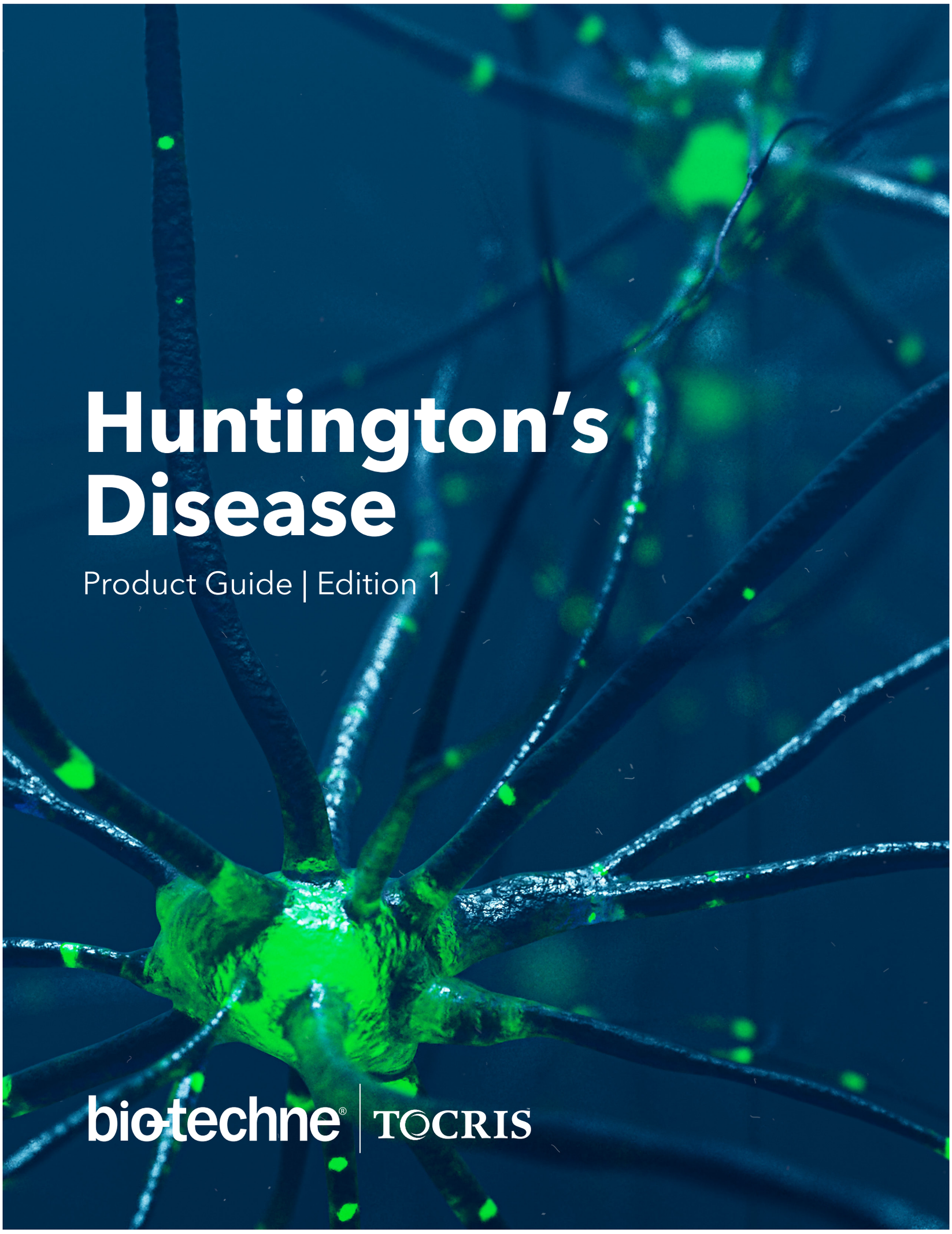

Huntington's Disease

Product Guide | Edition 1

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Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease. It is characterized by cognitive decline, psychiatric disturbances and motor dysfunction – predominantly chorea, an involuntary movement disorder. These symptoms are thought to result from the cellular stress caused by mutant huntingtin (mHTT) mRNA and protein. Although huntingtin protein (HTT) is ubiquitously expressed, medium spiny neurons (MSNs) in the basal ganglia of the striatum exhibit particular vulnerability to mHTT. Consequently, MSNs are the first cells to be lost, with the neurodegeneration later progressing throughout the striatum and frontal cortex. There are no disease-modifying therapies currently available for HD; the only current FDA-approved drugs for HD are the reversible inhibitors of vesicular monoamine transporter type 2 (VMAT2): Tetrabenazine (Cat. No. 2175), and Deutetrabenazine. Mood stabilizers, such as antidepressants (Prozac/Fluoxetine, Cat. No. 0927) and atypical antipsychotics (Risperidone, Cat. No. 2865) are also commonly prescribed to Huntington's disease patients. Current research is focused on the identification of new therapeutic targets, with a great deal of interest in discovering disease-modifying therapies rather than simply symptomatic treatments. A brief insight into this research is described here.

Genetics 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 transcriptional regulation, 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 the expansion reaches above the tolerated threshold of 35 CAG repeats, the gene encodes for an mHTT transcript and protein. mHTT not only lacks the function of the wild-type HTT but also has entirely different characteristics.

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 which requires 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, although this research has yet to translate into therapies that can 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 1**.

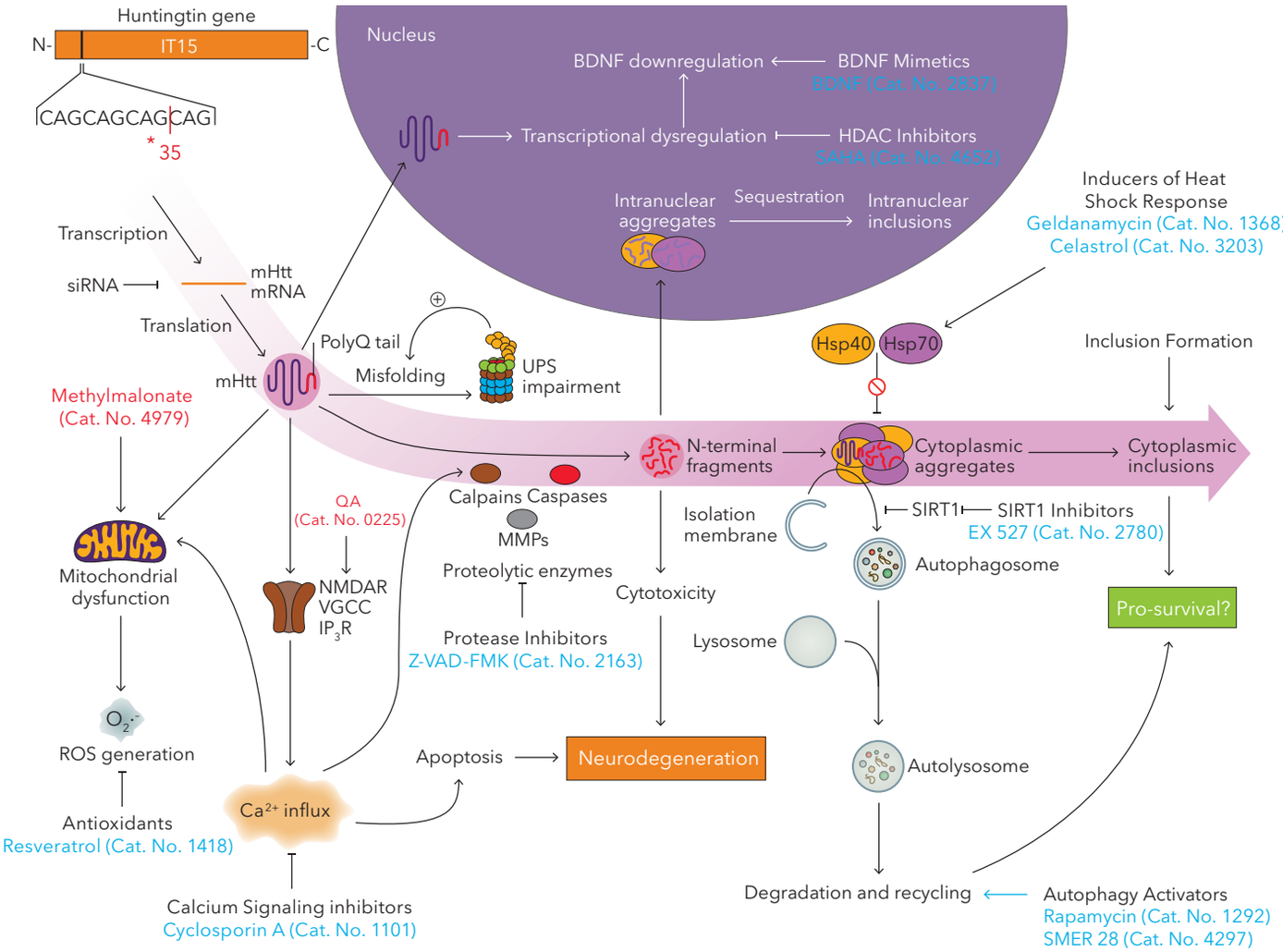
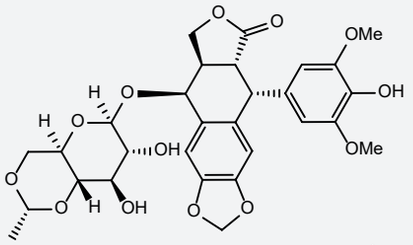


FIGURE 1: Therapeutic interventions in Huntington's disease. Huntingtin protein synthesis and processing is integral to HD pathology. mHTT is generated by translation of an allele containing over 35 CAG repeats. It is processed by proteolytic enzymes (namely calpains, caspases and MMPs) to generate toxic 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; inducers of heat shock response; histone deacetylase (HDAC) inhibitors; promoters of inclusion formation; and small interfering RNA (siRNA) (examples shown in blue). Small molecules have also been used to generate toxin models of HD (examples shown in red). Abbreviations: BDNF - brain-derived neurotrophic factor; Hsp40 - heat shock protein 40; Hsp70 - heat shock protein 70; IP3R - IP3 receptor; MMPs - matrix metalloproteinases; NMDAR - NMDA receptor; QA - quinolinic acid; ROS - reactive oxygen species; UPS - ubiquitin-proteasome system; VGCC - voltage-gated calcium channel.

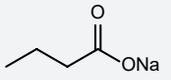
Somatic Instability

The term somatic instability describes the progressive expansion of the CAG repeat region within somatic cells over time. MSNs display one of the highest levels of somatic instability across cell types, which may explain the vulnerability of MSNs to HD pathology. The mismatch DNA repair system has been strongly implicated in somatic instability and has been proposed to be the mechanism by which the incremental increase in CAG repeats occurs over time. During DNA replication and transcription, mismatched hairpins/loops can form within the CAG repeat region and are recognized by the mismatch DNA repair proteins. However, during the repair reaction, the loops become incorporated into the gene sequence. Every time this erroneous mismatch repair occurs in cells, the CAG repeat region grows further. Many different repair proteins have been demonstrated to influence the rate of somatic instability, including the complex of nuclease FAN1, MSH2 and MSH3 (MutSβ), DNA topoisomerase and tyrosyl-DNA phosphodiesterase. Therefore, DNA topoisomerase inhibitors Etoposide (Cat. No. 1226) and CPT 11 (Cat. No. 2688) may be of interest in investigating modulation of somatic instability in HD research models. Studies in both *in vitro* and *in vivo* models have reported the ability of histone deacetylase (HDAC) inhibitors to induce CAG repeat contraction within the HTT gene (see **Box 1**).

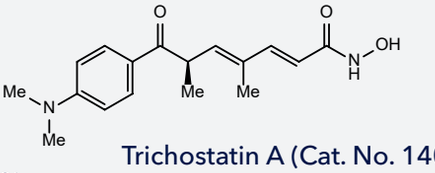
Box 1 DNA repair (DNA topoisomerase inhibitors and histone deacetylase inhibitors)



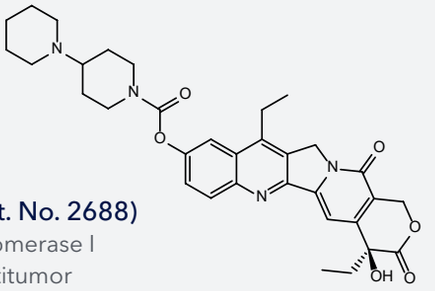
Etoposide (Cat. No. 1226)
Topoisomerase II inhibitor



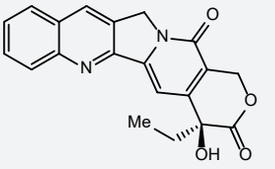
Sodium butyrate (Cat. No. 3850)
Histone deacetylase inhibitor



Trichostatin A (Cat. No. 1406)
Potent histone deacetylase inhibitor



CPT 11 (Cat. No. 2688)
DNA topoisomerase I inhibitor; antitumor



Camptothecin (Cat. No. 1100)
Potent histone deacetylase inhibitor

mHTT mRNA and Protein

The abnormally long CAG sequence and polyglutamine tract in the mHTT mRNA and protein, respectively, results in mHTT forming an abnormal tertiary structure which then aberrantly sequesters proteins. Due to the promiscuous nature of this action, mHTT mRNA and protein are able to disrupt numerous processes within the cell, such as nuclear transport, transcription, translation, mitochondrial activity and synaptic transmission. This dysregulation activates the integrated stress response - the outcome of which is apoptosis that translates to atrophy within the striatum and cortex. For a summary of mHTT effects at the cellular level and the points of therapeutic interventions in HD, see **FIGURE 2**: Somatic instability.

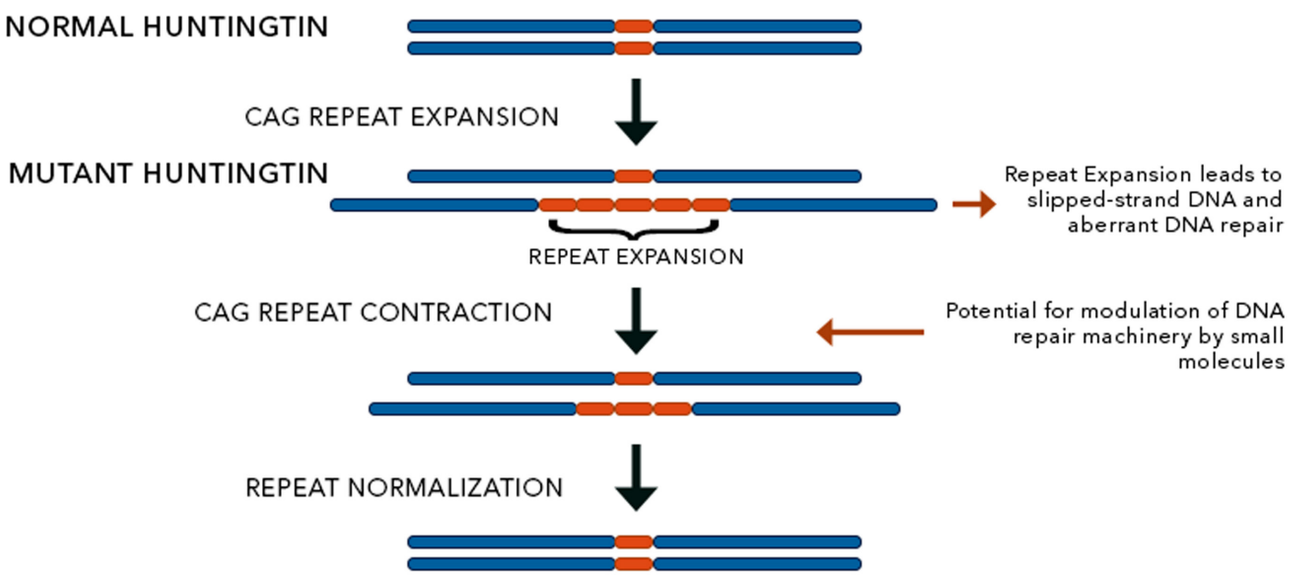


FIGURE 2: Somatic instability. Schematic summarizing CAG repeat expansion and instability in the mHTT gene and a potential therapeutic approach by targeting the DNA repair machinery. Adapted from Nakamori and Mochizuki (2021) Targeting expanded repeats by small molecules in repeat expansion disorders. Mov. Disord. 36 298.

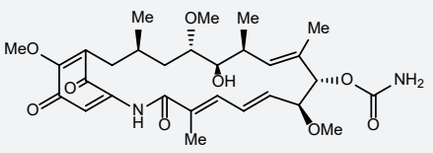
Proteolysis and Inclusion Bodies

Inclusion bodies are a pathological hallmark of HD and are usually observed in cells where mHTT is expressed. They consist of protein aggregates containing toxic N-terminal mHTT fragments, and are generated by the caspase, calpain and matrix metalloproteinase (MMP) enzymes within MSNs. These protein aggregates can be visualized using dyes, such as Thioflavin T (Cat. No. 7122), and often include numerous sequestered proteins, including ubiquitin and chaperone proteins. Nuclear aggregates consist mainly of the toxic N-terminal mHTT fragments (polyglutamine tract), while cytoplasmic inclusions contain both full length and truncated mHTT. It is as yet unclear whether inclusion bodies merely coincide with disease, or if they themselves are cytotoxic; several lines of evidence suggest that by sequestering diffuse mHTT fragments, inclusions may prolong cell survival. Greater understanding of the mechanisms behind mHTT processing and inclusion body formation may therefore help elucidate disease progression.

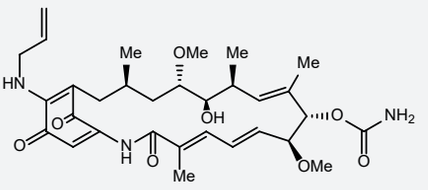
It has been suggested that the presence of cellular aggregates stimulates autophagy. Conversely, inhibition of autophagy increases both aggregate formation and soluble mHTT levels. A variety of autophagy-inducing compounds have shown efficacy in HD models. For example Rapamycin (Cat. No. 1292) inhibits mTOR, a negative regulator of autophagy that is sequestered into aggregates. Rapamycin has been shown to lower mHTT accumulation in cellular models and to protect against neurodegeneration in a fly model of HD. SMER 28 (Cat. No. 4297), a regulator of autophagy, 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 Class III histone deacetylase Sirtuin 1 (SIRT1) prevents autophagic degradation of mHTT by removing its acetyl tags. Selective SIRT1 inhibitors, such as EX 527 (Cat. No. 2780) and AK 7 (Cat. No. 4754), may therefore aid mHTT degradation via autophagy and increase its clearance. Deacetylation of regulatory transcription factors by SIRT1 also promotes the expression of neuroprotective genes and brain-derived neurotrophic factor (BDNF, Cat. No. 2837).

mHTT protein is subject to misfolding as a result of its abnormally long polyglutamine tract. Chaperone proteins (or heat shock proteins) are of interest in HD research, since they re-fold misfolded proteins and can suppress the generation of toxic N-terminal fragment oligomers that later form aggregates. There are three chaperones that are significant 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 HTT, aiding its clearance by the ubiquitin-proteasome system (UPS). Hsp90 inhibition, by compounds such as 17-AAG (Cat. No. 1515), 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. Hsp70 activators and inducers such as BGP 15 (Cat. No. 6703) may also be useful tools. (**Box 2**)

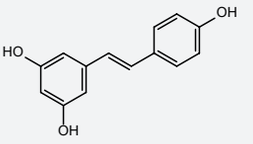
Box 2 Heat shock proteins



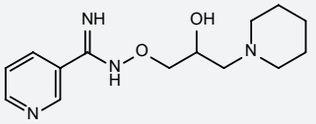
Geldanamycin (Cat. No. 1368)
Selective Hsp90 inhibitor



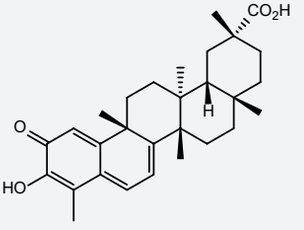
17-AAG (Cat. No. 1515)
Selective Hsp90 inhibitor



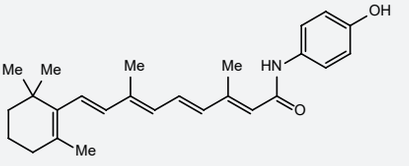
Resveratrol (Cat. No. 1418)
Cyclooxygenase inhibitor



BGP 15 (Cat. No. 6703)
PARP inhibitor; cytoprotectant



Celastrol (Cat. No. 3203)
Inhibits TNF-α-induced NF-κB activation



Fenretinide (Cat. No. 1396)
Synthetic retinoid; antiproliferative and antioxidant

Transcriptional Dysregulation

mHTT and its N-terminal 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 histone acetyltransferase activity can be countered by use of HDAC inhibitors, such as Sodium butyrate (Cat. No. 3850) and Trichostatin A (Cat. No. 1406), which both slow disease progression in HD mouse models.

Transcriptional dysregulation affects levels of BDNF and its receptor, TrkB, both of which may be 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 via upstream and downstream pathways may be therapeutically viable options. The σ-1 receptor activators, PRE-084 (Cat. No. 0589) and NE 100 (Cat. No. 3133) have been demonstrated to increase BDNF levels in HD research models, with this translating to slower disease progression. Infusion of recombinant BDNF, use of cell grafts releasing BDNF, and BDNF mimetics are all potential strategies undergoing research. TrkB receptors may be transactivated by adenosine A2A 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, 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. Methylmalonate (Cat. No. 4979), which inhibits succinate dehydrogenase (mitochondrial complex II), induces neuronal cell death and has been used to generate HD models.

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, and the accumulation of ROS can trigger ferroptosis, resulting in cell death. The ferroptosis inhibitors Liproxstatin-1 (Cat. No. 6113) and Zileuton (Cat. No. 3308) have been reported to protect neurons against mitochondrial dysfunction in HD rodent models. The antioxidants Fenretinide (Cat. No. 1396) and Resveratrol (Cat. No. 1418), have been shown to improve cell survival and exhibit neuroprotective activity, respectively, in two different HD models (**Box 2**). This activity is thought to result from the activation of ERK by these two compounds. The antioxidant Fisetin (Cat. No. 5016) has also been shown to reduce neurodegeneration in flies, and increase median lifespan of flies and mice expressing mHTT. 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 glutamine expansion, and increases neuronal survival *in vitro*. Consequently, Nrf2 is a key contributor to mHTT clearance so activators of Nrf2, such as CDDO Im (Cat. No. 4737) and RA 839 (Cat. No. 5707) may be useful tools.

Nuclear-Cytoplasmic Transport Interference

In contrast to wild-type huntingtin, mHTT is able to inappropriately sequester RanGAP – a GTPase and GTP-binding nuclear protein involved in nucleocytoplasmic transport. Along with the nucleoporins NUP62 and NUP88, and Ran (Ras-related nuclear protein), the transport between nucleus and cytosol are regulated. However, mHTT prefentially binds to RANGAP1 and interferes with the transport of cargo between nucleus and cytoplasm. The result of the aberrant transport is a neurotoxic nuclear pore complex and protein mislocation within the cell. Selective inhibitors of nuclear export (SINE) may be useful tools in rescuing this pathology and have been successful in rescuing this deficit in HD cellular models.

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 adds to their selective vulnerability 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.

The rate of glutamate uptake has been shown to be inversely related to the number of CAG repeats; in HD brain tissues, glutamate uptake and, therefore, clearance from the synaptic cleft are low. 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. In addition, NMDA receptor-positive allosteric modulators have been reported to improve the cognitive deficits that emerge in the early stages of HD progression. However, the glutamate release inhibitor Riluzole (Cat. No. 0768) showed no beneficial effects in a phase III HD trial.

Dopamine

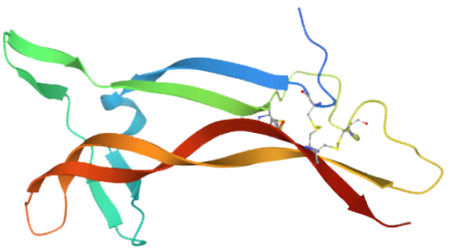
Dopamine is thought to act synergistically with glutamate to increase Ca^{2}+ levels, sensitizing striatal neurons to mHTT toxicity and inducing apoptosis in MSNs. High doses of dopamine can also induce death of striatal neurons, likely via oxidative stress. Administration of the dopamine precursor L-DOPA (Cat. No. 3788) consistently elevates dopamine levels and increases loss of MSNs in HD mice, as well as exacerbating dyskinetic symptoms in HD patients. Motor dysfunction and MSN loss is also evident in dopamine transporter knockout mice, which have consistently high dopamine levels.

The reversible VMAT2 inhibitors are the only FDA approved treatments for HD. VMAT2 inhibitors, including Tetrabenazine (Cat. No. 2175), are believed to improve motor function by depleting dopamine storage vesicles, but exhibit some serious side-effects, including depression due to decreased 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 the study of a variety of diseases, including neurodegenerative disorders. With regard to HD research, induced pluripotent stem cells (iPSCs) are of particular interest as they can be readily derived from patient somatic cells. These patient-derived iPSC lines contain the precise disease mutation seen in the patient, providing a robust and translatable *in vitro* disease model. As a result of their ability to self-renew, stem cells provide researchers with an unlimited source of cells for drug screening, disease modeling and cell replacement therapy, following differentiation into the cell type of interest, e.g. MSNs.

Neuronal differentiation of stem cells can be achieved with a range of small molecules (**Box 3**). The synthetic retinoid EC 23 (Cat. No. 4011) and glycogen synthase kinase-3β inhibitor TWS 119 (Cat. No. 7405) can both induce neuronal differentiation in embryonic stem cells (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. The use of small molecules to generate specific cell types from stem and progenitor cells opens up possibilites 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 shown to reduce loss of striatal neurons and lower the number of mHTT aggregates in a quinolinic acid-lesioned rat model.



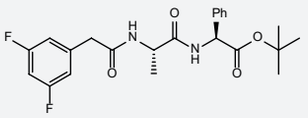
BDNF (Cat. No. 2837)
Activates TrkB and p75 receptors

Image adapted from RSCB Protein Data Bank (http://www.rcsb.org). PDB ID: 1B8M Robinson *et al.* (1999) Protein Sci. 8 2589. PMID: 10631974

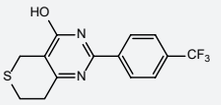
Over the last few decades many reproducible and efficient methods of generating MSNs from ESC/iPSC lines have been developed. This includes both extrinsic cue directed (i.e. small molecule induction factors) or intrinsic cue directed (i.e. enforced expression of lineage-determining transcription factors) differentiation paradigms. A highly efficient, and well-established extrinsic cue paradigm for generating MSNs has been reported that uses two small molecules, SB 431542 (Cat. No. 1614) and LDN 193189 (Cat. No. 6053) to inhibit SMAD signaling pathways (so called dual SMAD

inhibition method) to drive neurogenesis of pluripotent stem cells. Further regionalization of the neuroepithelial cells to MSN lineage is obtained by adding XAV 939 (Cat. No. 3748) and Activin A. Methods to efficiently generate more mature neuronal cultures *in vitro* using a cocktail of small molecules have also been reported. These include cell cycle inhibitors DAPT (Cat. No. 2634) and PD 0332991 (Cat. No. 4786); neurogenic/neurotrophic factors L-Ascorbic acid (Cat. No. 4055), BDNF (Cat. No. 2837) and LM 22A4 (Cat. No. 4607); and other factors known to directly influence neuronal physiology, including GABA (Cat. No. 0344), CHIR 99021 (Cat. No. 4423) and Forskolin (Cat. No. 1099), (see **Box 3**).

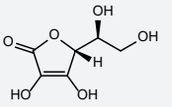
Box 3 Stem Cells



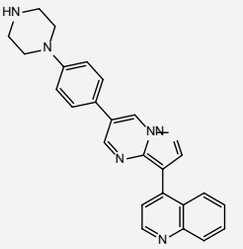
DAPT (Cat. No. 2634)*
γ-secretase inhibitor; induces neuronal differentiation; blocks Notch signaling



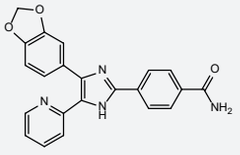
XAV 939 (Cat. No. 3748)^
Potent tankyrase inhibitor



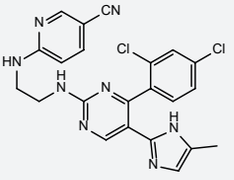
L-Ascorbic acid (Cat. No. 4055)
Enhances the generation of iPSCs; increases reprogramming efficiency



LDN 193189 (Cat. No. 6053)*
Potent and selective ALK2 and ALK3 inhibitor; inhibits BMP4 signaling; promotes neural induction of hPSCs



SB 431542 (Cat. No. 1614)^
Potent, selective inhibitor of TGF-βRI, ALK4 and ALK7



CHIR 99021 (Cat. No. 4423)^
Highly selective GSK-3 inhibitor; acts as Wnt activator

(* = also available as Ancillary Material Grade, ^ = also available as GMP)

Regenerative Medicine

iPSC or ESC-derived MSN progenitors are a valuable resource for regenerative medicine and have been shown to correct motor problems in quinolinic acid-lesioned mice. Cell replacement therapy has been proposed as a therapeutic strategy in patients with HD. However, *in vitro* derived MSN progenitor grafts often fail to match the efficacy of primary MSNs from the lateral ganglionic eminence in HD *in vivo* research models. Graft survival and functional connectivity are two major hurdles that *in vitro* derived grafts typically fall short on. Further optimization of differentiation protocols to obtain more authentic MSNs from pluripotent stem cells should hopefully lead to more success in this field over the coming years.

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) 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 increases median lifespan of flies and mice expressing mHTT.

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 be useful tools for studying the role of ERK in HD pathology.

Psychiatric Symptoms

Antidepressants (mainly selective serotonin reuptake inhibitors, SSRIs) and antipsychotics may 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 also raise BDNF levels. Certain SSRIs have also been shown to increase neurogenesis, motor control and cognitive ability in mouse HD models. For example, it has been found that Fluoxetine (Cat. No. 0927) improves cognitive function in transgenic HD mice, as well as improving neurogenesis by increasing neuronal differentiation of proliferating cells.

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. Although they show similar neurodegenerative mechanisms, HD differs from Alzheimer's disease and Parkinson's disease in that it is a monogenetic disorder. As a result of this, gene silencing approaches using small interfering RNAs (siRNAs) and antisense oligonucleotides to selectively target the messenger RNA (mRNA) encoded by the mutant allele are of great interest as disease-modifying therapy. This approach for the treatment of HD has reached phase III clinical trials.

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 disorders with similar pathologies, with HD being just one of 12 known CAG repeat disorders.

List of Acronyms

Acronym	Definition
BDNF	Brain-derived neurotrophic factor
CBP	CREB-binding protein
CREB	cAMP response element-binding protein
ESC	Embryonic stem cell
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
HD	Huntington's disease
HDAC	Histone deacetylase
Hsp40	Heat shock protein 40 (DNAJ)
Hsp70	Heat shock protein 70
Hsp90	Heat shock protein 90
HTT	Huntingtin protein
iPSC	Induced pluripotent stem cell
KMO	Kynurenine 3-monooxygenase
mHTT	Mutant huntingtin
MMP	Matrix metalloproteinase
mRNA	Messenger RNA
MSH2	DNA mismatch repair protein MutS Homolog 2
MSH3	DNA mismatch repair protein MutS Homolog 3
MSN	Medium spiny neuron
mTOR	Mammalian target of rapamycin
NMDAR	NMDA receptor
ROS	Reactive oxygen species
SINE	Selective inhibitors of nuclear export
siRNA	Small interfering RNA
SIRT1	Sirtuin 1
VMAT	Vesicular monoamine transporter
wt	Wild-type

Product List

Category	Cat. No.	Product Name	Primary Action
$5HT_{2A}$ Receptors			
Antagonists	2865	Risperidone	5-HT_{2A} antagonist; also D_2 antagonist; atypical antipsychotic
5-HT Transporter			
Inhibitors	0927	Fluoxetine	5-HT reuptake inhibitor
	1427	Citalopram	Highly potent and selective 5-HT uptake inhibitor
Adenosine A_{2A} Receptors			
Agonists	1063	CGS 21680	A_{2A} agonist
Antagonists	2270	SCH 58261	Potent, highly selective A_{2A} antagonist
Antioxidants			
Other	4055	L-Ascorbic acid	Enhances the generation of iPSCs; increases reprogramming efficiency
	3203	Celastrol	Inhibits TNF-α-induced NF-κB activation
Autophagy			
Activators	1292	Rapamycin	mTOR inhibitor; immunosuppressant
	4297	SMER 28	Positive regulator of autophagy
	0654	Verapamil	$Ca_V1.x$ blocker; induces autophagy
Inhibitors	1130	LY 294002	Prototypical PI 3-kinase inhibitor; also inhibits other kinases
	3982	Mdivi 1	Selective dynamin inhibitor; attenuates mitochondrial division and apoptosis
Calpains			
Inhibitors	1748	MG 132	Proteasome and calpain inhibitor. Inhibits NF-κB activation
Caspases			
Inhibitors	2163	Z-VAD-FMK	Cell-permeable, irreversible caspase inhibitor
Cathepsin			
Inhibitors	5208	E 64	Potent and irreversible cysteine protease inhibitor
	1190	Pepstatin A	Selective and high affinity cathepsin D inhibitor
Deubiquitinating Enzymes			
Inhibitors	4285	HBX 41108	Selective USP7 inhibitor
	4482	PR 619	Broad spectrum DUB inhibitor
DNA Topoisomerase			
Inhibitors	1100	Camptothecin	DNA topoisomerase inhibitor
	2688	CPT 11	DNA topoisomerase I inhibitor; antitumor
	1226	Etoposide	Topoisomerase II inhibitor
Dopamine			
Other	3788	L-DOPA	Dopamine precursor
Dynamin			
Inhibitors	2897	Dynasore	Non-competitive dynamin inhibitor
	6897	P110	Dynamin-related protein 1 (Drp1) inhibitor; cell-permeable

Category	Cat. No.	Product Name	Primary Action
ERK			
Inhibitors	4842	BIX 02189	Selective MEK5 and ERK5 inhibitor
	3706	FR 180204	Selective ERK inhibitor
Ferroptosis			
Inhibitors	6113	Liproxstatin-1	Potent ferroptosis inhibitor
	3308	Zileuton	5-LOX inhibitor; also inhibits ferroptosis; orally bioavailable
Fluorescent Dyes			
Other	7122	Thioflavin T	Fluorescent dye; binds to amyloid fibrils
GABA			
Agonists	0344	GABA	Endogenous agonist
Glutamate Group I Receptors			
Agonists	0805	(S)-3,5-DHPG	Selective group I mGlu agonist; active enantiomer of 3,5-DHPG (Cat. No. 0342)
Antagonists	2333	JNJ 16259685	Highly potent, mGlu1-selective non-competitive antagonist
	2921	MTEP	Potent and selective $mGlu_5$ antagonist
Other	0768	Riluzole	Inhibits glutamate release; also GABA uptake inhibitor
	1611	Lamotrigine	Inhibits glutamate release. Anticonvulsant
Glutamate Transporter			
Inhibitors	0111	Dihydrokainic acid	EAAT2 (GLT-1)-selective non-transportable inhibitor of L-glutamate and L-aspartate uptake
Heat Shock Proteins			
Inhibitors	1515	17-AAG	Selective Hsp90 inhibitor
	1368	Geldanamycin	Selective Hsp90 inhibitor
	2653	Pifithrin-μ	Inhibitor of p53-mitochondrial binding; also inhibits Hsp70 activity
	3803	VER 155008	Hsp70 inhibitor
Hsp70 activators	6703	BGP 15	PARP inhibitor; cytoprotectant; also activates Hsp70
Histone Acetyltransferase			
Inhibitors	6387	A 485	Potent and selective p300/CBP inhibitor; orally bioavailable
	7366	WM 3835	Lysine acetyltransferase HBO1 (KAT7) inhibitor
Histone Deacetylases			
Class I inhibitors	3515	FK 228	Potent and selective class I histone deacetylase inhibitor; antitumor
Class II inhibitors	3402	Tubacin	HDAC6 inhibitor; inhibits α-tubulin deacetylation
Class III inhibitors	4754	AK 7	Selective SIRT2 inhibitor; brain penetrant
	2780	EX 527	Selective SIRT1 inhibitor
Class III activators	1418	Resveratrol	Cyclooxygenase inhibitor; also SIRT1 activator
Non-selective HDAC inhibitors	3850	Sodium butyrate	Histone deacetylase inhibitor
	1406	Trichostatin A	Potent histone deacetylase inhibitor
	4652	SAHA	Class I and II HDAC inhibitor

Product List

Category	Cat. No.	Product Name	Primary Action
IP_3 Receptors			
Antagonists	1224	2-APB	IP_3 receptor antagonist. Also TRP channel modulator
Other	6210	ci-IP3/PM	Caged inositol triphosphate
	1280	(-)-Xestospongin C	Reported inhibitor of IP_3-dependent Ca^{2+} release
JNK/c-Jun			
Inhibitors	4924	CEP 1347	Inhibitor of JNK signaling
	1496	SP 600125	Selective JNK inhibitor
Kinases			
Activators	2864	Metformin	AMPK activator; antidiabetic agent
Inhibitors	4786	PD 0332991 isethionate	Potent cdk4 and cdk6 inhibitor; brain penetrant
	4423	CHIR 99021	Highly selective GSK-3 inhibitor; acts as Wnt activator; promotes reprogramming of fibroblasts to iPSCs
	7405	TWS 119	Potent GSK3 inhibitor; induces neuronal and CD8(+) T cell differentiation
MPTP			
Inhibitors	1101	Cyclosporin A	Calcineurin inhibitor; also inhibits MPTP opening
Other	2906	TRO 19622	Binds voltage-dependent anion channel (VDAC); thought to inhibit MPTP opening
Neural Stem Cells			
Other	2634	DAPT	γ-secretase inhibitor; induces neuronal differentiation; blocks Notch signaling
	1141	Dibutyryl-cAMP, sodium salt	Cell-permeable cAMP analog
	3093	Dorsomorphin	Potent AMPK inhibitor; also BMP type I receptor inhibitor
	1099	Forskolin	Adenylyl cyclase activator
	6053	LDN 193189	Potent and selective ALK2 and ALK3 inhibitor; inhibits BMP4 signaling; promotes neural induction of hPSCs
	3044	PD 173074	FGFR1 and -3 inhibitor
	4366	SAG	Potent Smoothened receptor agonist; activates the Hedgehog signaling pathway
	1254	Y-27632	Selective ROCK inhibitor; improves survival of ESCs and iPSCs; also used in neural differentiation protocols
	4439	ISX 9	Neurogenic agent; induces neuronal and cardiomyogenic differentiation
Inhibitors	1614	SB 431542	Potent, selective inhibitor of TGF-βRI, ALK4 and ALK7
Neuronal Metabolism			
Other	2568	MOG (35-55)	Encephalitogenic myelin oligodendrocyte glycoprotein fragment
	2567	PLP (139-151)	Encephalitogenic myelin proteolipid fragment
NMDA Receptors			
Agonists	0225	Quinolinic acid	Endogenous NMDA agonist and transmitter candidate
Antagonists	0924	(+)-MK 801 maleate	Non-competitive NMDA antagonist; acts at ion channel site

Category	Cat. No.	Product Name	Primary Action
Nrf2			
Activators	4737	CDDO Im	Nrf2 signaling activator
	5707	RA 839	Nrf2 activator; inhibits Nrf2/Keap1 interaction
Other Dehydrogenase Inhibitors			
Inhibitors	4979	Methylmalonate	Succinate dehydrogenase inhibitor
Post-translational Modifications			
Inhibitors	2430	GGTI 298	Geranylgeranyltransferase I (GGTase I) inhibitor
	6326	Ginkgolic acid	Inhibits SUMOylation by binding E1
	6265	Lonafarnib	Potent farnesyltransferase inhibitor
Proteasome			
Inhibitors	2267	Lactacystin	Cell-permeable, potent and selective proteasome inhibitor
	1748	MG 132	Proteasome and calpain inhibitor. Inhibits NF-κB activation
	6033	(R)-MG 132	Potent 20S proteasome inhibitor
Protein Disulfide Isomerases			
Inhibitors	5116	PACMA 31	Irreversible protein disulfide isomerase (PDI) inhibitor
Protein Ser/Thr Phosphatases			
Inhibitors	1336	Calyculin A	Protein phosphatase 1 and 2A inhibitor
	3631	FK 506	Potent calcineurin inhibitor; immunosuppressant
	3657	Sal 003	Cell-permeable inhibitor of eIF2α dephosphorylation
Reductases			
Inhibitors	3254	Ro 61-8048	Potent kynurenine 3-monooxygenase (KMO) inhibitor
Retinoic Acid Receptors			
Other	1396	Fenretinide	Synthetic retinoid; antiproliferative and antioxidant
	4011	EC 23	Synthetic retinoid; induces differentiation of stem cells
σ1 Receptor			
Agonists	0589	PRE-084	Highly selective σ1 agonist
Antagonists	3133	NE 100	Selective σ1 antagonist
Tankyrase			
Inhibitors	3748	XAV 939	Potent tankyrase inhibitor
TRK Receptors			
Agonists	2837	BDNF (human)	Activates TrkB and p75 receptors
	4607	LM 22A4	Potent TrkB agonist
Inhibitors	4559	GNF 5837	Potent Trk inhibitor; inhibits TrkA, TrkB and TrkC
Vesicular Monoamine Transporters			
Inhibitors	2742	Reserpine	Inhibitor of vesicular monoamine transport
	2175	Tetrabenazine	Potent inhibitor of vesicular monoamine transport
Other	5043	FFN 206	Fluorescent VMAT2 substrate
	6717	FFN 270	Fluorescent substrate for NET and VMAT2

Further Reading

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

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Crook and Housman (2011) Huntington's disease: can mice lead the way to treatment? *Neuron* **69** 423

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Goold *et al* (2021) FAN1 controls mismatch repair complex assembly via MLH1 retention to stabilize CAG repeat expansion in Huntington's disease. *Cell Rep.* **36** 109649

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Labbadia and Morimoto (2013) Huntington's disease: underlying molecular mechanisms and emerging concepts. *Trends Biochem. Sci.* **38** 378

Landles and Bates (2004) Huntingtin and the molecular pathogenesis of Huntington's disease. Fourth in Molecular Medicine Review Series. *EMBO Rep.* **5** 958

Motawe *et al* (2020) PRE-084 as a tool to uncover potential therapeutic applications for selective sigma-1 receptor activation. *Int. J. Biochem. Cell. Biol.* **126** 105803

Perrier and Peschanski (2013) How can human pluripotent stem cells help decipher and cure Huntington's disease? *Cell Stem Cell* **11** 153

Ravikumar *et al* (2004) Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. *Nat. Genet.* **36** 585

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Telezhkin *et al* (2016) Forced cell cycle exit and modulation of GABAA, CREB, and GSK3β signaling promote functional maturation of induced pluripotent stem cell-derived neurons. *Am. J. Physiol. Cell Physiol.* **310** C520

Yin *et al* (2016) Mitochondria-targeted molecules MitoQ and SS31 reduce mutant huntingtin-induced mitochondrial toxicity and synaptic damage in Huntington's disease. *Hum. Mol. Genet.* **25** 1739

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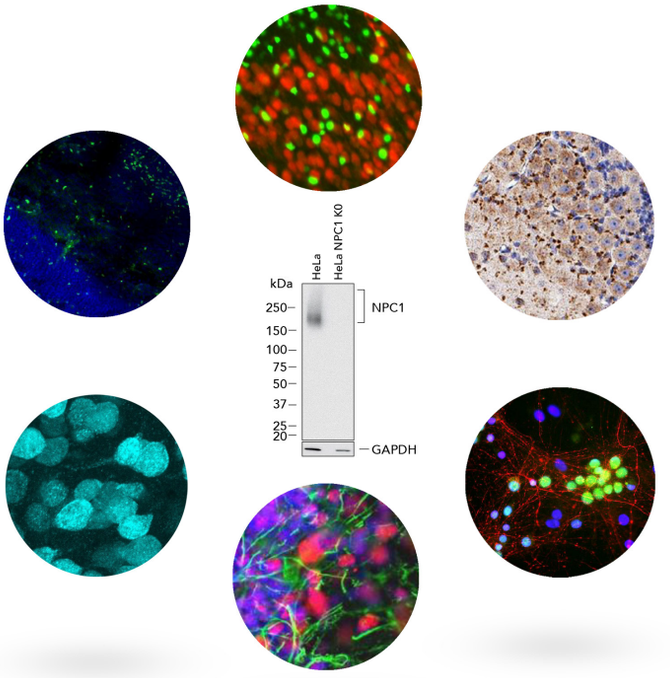

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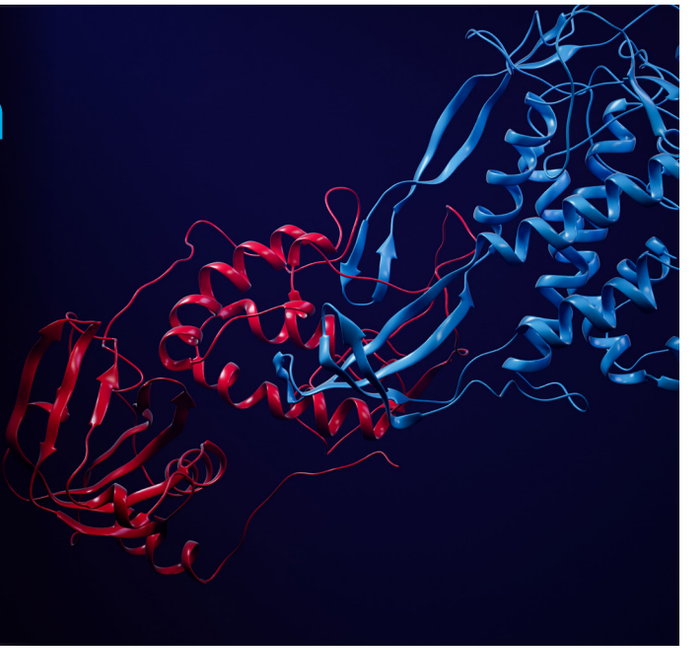

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