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Huntington's Disease: New Frontiers in Therapeutics

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Abstract

Purpose of Review This article describes and discusses new potential disease-modifying therapies for Huntington's disease that are currently in human clinical trials as well as promising new therapies in preclinical development.

Recent Findings Multiple potential disease-modifying therapeutics for HD are in active development, including direct DNA/gene therapies, RNA modulation, and therapies targeted at aberrant downstream pathways.

Summary The etiology of Huntington's disease (HD) is well-known as an abnormally expanded trinucleotide repeat within the huntingtin gene. However, the pathogenesis downstream of the mutant huntingtin gene is complex, involving multiple toxic pathways, including abnormal protein fragmentation and neuroinflammation. The current treatment of HD focuses largely on symptomatic management. This article discusses new, potential disease-modifying therapies that are currently in human clinical trials and preclinical development.

Keywords Huntington's disease · RNA interference · Gene therapy · Clinical trials · Disease-modifying therapy

Introduction

Huntington's disease (HD; OMIM 613004) is an autosomal dominant, neurodegenerative disorder, characterized by distinct abnormal movements, psychiatric symptoms, and cognitive deficits. Worldwide prevalence of HD is 2.7/100,000, with epidemiological studies in Europe, North America, and Australia (5.7/100,000) showing higher prevalence than in Asia (0.4/100,000) [1]. The genetic mutation in HD has been well-established as a pathogenic expansion (≥ 36 repeats) of a trinucleotide repeat, cytosine-adenine-guanine (CAG), in the huntingtin (HTT) gene, located on chromosome 4 [2]. Early studies in transgenic mice showed abnormal proteinaceous aggregates of mutant huntingtin protein (mHTT), which were later also detected in brains of patients with Huntington's disease [3–5]. Subsequent studies of neurotransmitter receptor levels in transgenic mice expressing mHTT revealed that transcriptional dysregulation may play an early role in HD pathogenesis [6]. Since then, many studies have implicated mHTT in several pathways leading to HD pathogenesis, including direct damage/aggregation, altered transcription of essential genes, induction of excitotoxicity at cortico-striatal synapses activating cell death pathways, impaired astrocyte-medium spiny neuron homeostasis, mitochondrial dysfunction, and aberrant immune activation [7].

Current treatment of HD focuses largely on symptomatic management of chorea and psychiatric and cognitive symptoms. Tetrabenazine and deutetrabenazine have been shown to effectively reduce chorea in HD and are the only agents FDA-approved for the treatment of HD [8, 9]. Neuroleptics are also commonly used off-label for treatment of chorea as well as psychosis related to HD [10]. Other psychiatric symptoms of HD, such as depression, anxiety, and agitation, are treated with SSRI/SNRIs and benzodiazepines, and dementia related to HD can be treated with acetylcholinesterase inhibitors [10] though with limited success. There is no FDA-approved disease-modifying treatment for HD at this time. Many exciting preclinical studies and clinical trials are evaluating potential disease-modifying treatments for HD. This article will focus on ongoing clinical trials and preclinical studies that aim to identify disease-modifying therapies for HD.

Although there is one underlying pathogenic gene in HD, the downstream pathways leading to neuronal cell death in HD are complex and not completely understood. Mutant HTT protein (mHTT) differs from wild-type HTT protein by

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an elongated polyglutamine (polyQ) tract near the amino terminus of the HTT protein. Mutant HTT transcripts produce toxicity through gain-of-function interruption of multiple downstream pathways including inducing synaptic excitotoxicity at the striatal-cortical junction involving medium spiny neurons (MSNs), aberrant immune activation, alteration of transcription in essential genes, reduction of neurotrophic factors such as BDNF, and mitochondrial dysfunction [7, 11]. Major drug developments and ongoing investigational drugs target different stages of HD pathogenesis, including direct gene editing, modulation of transcription or RNA transcripts, and correction of aberrant downstream pathways. The following sections will discuss each of these new therapies in further detail.

Therapies Targeted at Gene Transcript and Gene

As the toxic and neurodegenerative pathogenesis of HD begins with an abnormal HTT gene and gene transcript (mHTT), it makes sense that disease-modifying therapy would directly target the mutant gene or immediate gene transcripts to lower the level of mutant HTT. Studies in mouse models have shown that suppression of mHTT or inactivation of the HTT gene can reverse HD-like behavioral and neuropathological phenotypes [12, 13]. Recently, therapies designed to lower HTT expression using antisense oligonucleotide or microRNA techniques have advanced to human clinical trials.

RNA-Targeted Therapies Antisense oligonucleotides (ASOs) lower HTT RNA transcripts by binding to an RNA-specific sequence of HTT that activates RNase H-mediated degradation. Non-selective ASO targets both wild-type and mutant HTT transcripts, whereas selective ASO targets only mutant allele HTT transcripts. The advantage of selective ASO is that it preserves wild-type HTT. A disadvantage is that in order for the ASO to be allele specific, selective ASOs are designed to target single nucleotide polymorphisms (SNPs) that are present in the mutant allele but not wild-type [14]. HD patients with different geographical origins express different SNPs, so a disadvantage of selective ASOs is that therapy is only effective in patients who express the particular SNP that is targeted [15]. Thus, the advantage of non-selective ASOs is its generalizability to all HD populations, with the disadvantage of also downregulating wild-type HTT transcripts. However, studies have shown that partial reduction of wild-type HTT does not cause changes in motor function or alterations in histopathological findings in both rodent and non-human primate studies [16]. Whether long-term reductions in wild-type HTT could have adverse consequences in adult patients remain unknown.

Two drugs are currently being investigated for HD using ASO technology. A non-selective ASO for the HTT transcript (Ionis-HTTrx) (clinicaltrials.gov, NCT02519036) has completed early phase clinical trials, and has now entered a large multicenter international efficacy trial. Phase I and IIa clinical trials completed in November 2017 were randomized, double-blind, placebo-controlled studies with the primary outcome measure of safety and secondary outcome measure of HTTRx pharmacokinetics. HTTRx or matching placebo was administered via intrathecal injection every 4 weeks for 4 doses at 5 concentrations in 46 patients with early manifest HD. The treatment was found to be safe, with no serious adverse events in the treatment group. HTTRx was measurable in the CSF of patients who received doses of 30 mg or more, with a plateau in the concentration in CSF over the 60-mg dose. Additional end points showed a dose-dependent reduction of mutant huntingtin concentrations in CSF, with ~40% reduction of mHTT at the 2 highest drug concentrations [17••].

Based on these findings, a phase III clinical trial of this non-selective ASO intrathecal treatment (RO7234292, or RG6042) to evaluate efficacy and safety has begun (clinicaltrials.gov, NCT03761849). This randomized, multicenter, double-blind, placebo-controlled study will follow subjects over 2 years, and will enroll 909 manifest HD patients in three arms: (1) RG6042 every 8 weeks, (2) RG6042 every 16 weeks, versus (3) placebo every 8 weeks via intrathecal injection. Primary outcome measures will be changed in composite Unified Huntington's Disease Rating Scale (cUHDRS) and change in total functional capacity (TFC) score at week 101. Secondary outcome measures will include additional clinical rating measures of motor and cognitive function, adverse events, concentration of RG4602, mHTT protein level and neurofilament light chain (NfL) level in CSF, and MRI measures of brain volumes. This clinical trial has been actively recruiting since January 2019, and estimated study completion date is August 2022.

Another ASO approach in human trials involves the use of two selective ASOs targeting the most commonly occurring SNPs in mutant HTT transcripts—WVE-120101 (PRECISION-HD1) and WVE-120102 (PRECISION-HD2) (clinicaltrials.gov, NCT03225833, NCT03225846). The study designs are randomized, double-blind, placebo-controlled, with the goal of enrolling 60 early, stage I, or stage II HD participants, to receive monthly intrathecal injections of drug versus placebo. Primary outcome measures are safety and tolerability, and secondary outcome measures are pharmacokinetics of drug in plasma and pharmacodynamics of mHTT in CSF and TFC. Other outcome measures are UHDRS, behavior assessments, and MRI brain imaging. A press release with preliminary results from the WVE-120102 trial (PRECISION-HD2) reported a reduction of mutant HTT in CSF by 12.4% compared to placebo without significant change in total HTT or NfL levels [18]. Additionally, it was announced that the drug has been well-tolerated up to a dose of 16 mg [19]. Results from PRECISION-HD1 have not been announced. Future trials will likely explore higher doses in an effort to achieve greater reductions in mHTT.

MicroRNAs (miRNAs) can lower HTT RNA transcripts by recruiting HTT mRNA to RNA-induced silencing complex (RISC), whereby the HTT mRNA is degraded. However, for therapeutic purposes, miRNAs need to be delivered through a vector, such as adeno-associated virus (AAV) or lentivirus. AAV9-miRNA delivered via direct intrastriatal administration have resulted in a therapeutic benefit in multiple HD mouse models and a sheep model [20–22•]. While peripheral intravenous administration of AAV9-miRNA in HD mouse models showed therapeutic benefit, peripheral administration in a primate model was ineffective [23–25]. Both selective and non-selective allele targeting is feasible with the AAV9-miRNA approach, but administration requires direct intrastriatal injection.

RNA interference (RNAi) approaches to lowering mHTT are also entering human trials. AMT-130 (rAAV5-miHTT), a miRNA directed against HTT, is in a phase I/II clinical trial (clinicaltrials.gov, NCT04120493). This trial will enroll 26 early manifest HD participants in a randomized, double-blind, sham surgery–controlled study of 3 cohorts—(1) intrastriatal administration of low dose rAAV5-miHTT, (2) intrastriatal administration of high dose rAAV5-miHTT versus (3) sham surgery. Primary outcome measures are safety and adverse events over 18 months, and secondary outcome measures will explore the duration of AMT-130 in brain (measured in CSF), mHTT, and NfL levels in CSF, MRI imaging of brain volumes, and clinical rating scales assessing motor, cognitive, psychiatric, and quality of life functions. Study enrollment started in September 2019, with estimated primary completion in December 2022 and study completion in May 2026.

Several other RNAi approaches are nearing human clinical trials. A stereotactically guided intracerebral injection of AAV1-delivered anti-HTT miRNA, which has been shown to be safe and well-tolerated in partially reducing HTT levels in the putamen of non-human primates [26], is likely to enter clinical trials with human patients soon. Another AAV1 delivery system (VY-HTT01), which has been shown to improve motor and behavioral phenotype in an HD transgenic mouse model [27], is also being developed. Preliminary studies in non-human primates have shown good safety and tolerability, and reduction of HTT mRNA in striatum and cortex [28]. VY-HTT01 is also expected to enter human clinical trials soon.

DNA-Targeted Therapies Direct DNA-targeted approaches are still in preclinical phases and include zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR/Cas9 system [29]. Zinc finger proteins (ZFPs) are DNA-binding elements that bind directly to the mutant HD gene allele and can block transcription of the mutant huntingtin gene with an abnormally expanded CAG repeat sequence [30]. In a transgenic HD mouse model, ZFPs with a repressor element directly introduced into the striatum were able to reduce mHTT levels and improve HD-like behavior [31]. Similarly, TALENs contain a DNA recognition domain made of amino acid repeats and a repressor or nuclease component, which can either prevent transcription or directly cleave DNA. TALEN constructs applied to fibroblasts derived from HD patients have been shown to reduce mHTT expression and aggregation [32]. The CRISPR/Cas9 system was derived from a bacterial immune system against viral infection, and allowed for direct DNA cleavage via binding of protospacer-adjacent motif (PAM) sequences, and guide RNA-based nuclease activity [29]. Application of CRISPR/Cas9 to HD patient–derived fibroblasts via cleavage of CAG repeats from the HTT gene resulted in the reduction of mHTT expression [33••]. In a transgenic HD mouse model, application of CRISPR/Cas9 to excise CAG repeats in the HTT gene resulted in reduced expression and aggregation of mHTT, as well as improved motor function [34••]. All these DNA-targeted therapies remain in preclinical phases and have limitations including off-target effects, difficulty in design, and risk of activating inflammation due to non-host elements, and require invasive administration.

Small-Molecule Modulators of RNA Delivery of these DNA- and RNA-altering therapies is invasive, requiring either intrathecal or direct intraparenchymal injection. Small molecules that downregulate HTT protein levels have been identified from stem cells of HD patients, and ongoing preclinical studies of these small-molecule modulators, administered as an orally bioavailable pill, have shown promise in reducing brain HTT levels in mice [35]. There are also preclinical studies looking at targeting specific transcription elongation cofactors required for regular DNA transcription through long-expanded CAG repeats [36]. Preclinical studies have shown that blocking these transcription factors in HD transgenic mouse models results in reduced HTT aggregation, improved lifespan, and delayed motor impairment, and suggest that these transcription factors are promising therapeutic targets [37••]. Another potential therapy directed at RNA splicing is using an exon-skipping technique. Cleavage of mHTT RNA by caspases has been shown to generate toxic fragments, and inhibition of these caspase-binding sites has been shown to improve motor and behavioral function in HD transgenic mouse model [38–40]. Exon-skipping ASO, which has been used in other neurodegenerative diseases such as Duchenne muscular dystrophy (eteplirsen) and spinal muscular atrophy (nusinersen), has shown promising proof-of-concept studies in HD transgenic mice, by using ASOs to promote exon 12 skipping to omit caspase cleavage sites [7, 41].

Therapies Targeted at Aberrant Downstream Pathways

Neuropathology of post-mortem brains of HD patients shows significant degeneration of the striatum and deeper layers of the cortex [42, 43]. Magnetic resonance imaging of brain in premanifest and early HD patients has revealed significant regional striatal volume loss, but also more widespread atrophy including both white- and gray matter [44]. Medium spiny neurons (MSNs) are the predominant neuron population in the striatum, and MSNs are critical to mediating signals from the cortex to output pathways in the basal ganglia. There are two main striatal output pathways, direct and indirect, which contain different MSN populations—the direct pathway contains MSNs which express D1 receptors and project to SNr and GPi, whereas the indirect pathway contains MSNs expressing D2 receptors that project to GPe [45]. In HD, there is early loss of indirect pathway MSNs (seen in presymptomatic and early-stage HD), and later loss of direct pathway MSNs [46]. This observation explains some of the clinical manifestations of HD, which often includes early hyperkinetic movements such as chorea, and can progress to bradykinesia and rigidity in late-stage HD. In HD, there is aberrant post-synaptic activation of pro-death pathway signaling at the cortico-striatal synapse. Several post-synaptic proteins have been implicated in this aberrant downstream signaling, including extrasynaptic NMDA receptors (GluN2B), sigma 1 receptors (SIG1R), post-synaptic density protein 95 (PSD95), and phosphodiesterase 10A (PDE10A) [7, 47]. In addition, pathogenic or mutant HTT activates chronic neuroinflammation, via activation of cytokines, oxidative stress, reactive astrocytes, and reactive microglia [48]. HD patients and HD rodent models demonstrate increased migroglial activation, elevated proinflammatory cytokines, and chemokines, which correlate with disease progression [49–53].

Pridopidine is a small molecule with high affinity for sigma 1 receptors (SIG1R). SIG1Rs are transmembrane proteins located at the endoplasmic reticulum-mitochondrial interface, and through interaction with inositol 1,4,5 triphosphate receptors (IP3Rs), modulate calcium ion transport to promote neuroprotection and plasticity [54, 55]. In HD mouse models, mutant HTT aberrantly binds to IP3Rs, causing tonic calcium ion leakage, which promotes apoptosis in MSNs [56, 57]. Preclinical studies of pridopidine in mouse models showed normalization of cellular membrane calcium levels, improved motor and psychiatric phenotypes, and increased BDNF levels, improved survival, and rescue of transcriptional deficits in the striatum [58–60]. Phase II and III clinical trials (HART [61], MermaiHD [62]) failed to show significant improvement of the primary outcome measure (modified UHDRS motor score), and a follow-up phase II clinical trial (PRIDE-HD) found no significant improvement in UHDRS total motor scores in the whole study population, though there was improvement in total motor score and dystonia in early-stage participants [63••]. Importantly, in a post hoc analysis, PRIDE-HD demonstrated a statistically significant benefit in total functional capacity at 52 weeks in subjects receiving pridopidine compared to those receiving placebo [64••]. These observations suggest that a definitive clinical trial to assess the potential disease-modifying effects of pridopidine in HD is warranted.

Semaphorin 4D is a transmembrane signaling molecule, which promotes B cell and dendritic cell activation [65]. In addition, SEMA4D promotes glial cell inflammatory transformation in the setting of neurodegenerative processes such as HD. Preclinical studies of a blocking monoclonal antibody to SEMA4D (pepinimab) in rodents have shown reduction of neuroinflammation and prevention of autoimmune encephalomyelitis [66]. In a transgenic HD mouse model, treatment with anti-SEMA4D showed reduced brain atrophy, improvement of cognition, and reduction of anxiety [67]. Good safety data for anti-SEMA4D was shown in a phase I clinical trial for multiple sclerosis [68]. SIGNAL, a phase II/III clinical trial of anti-SEMA4D (pepinemab), is evaluating safety and efficacy in early manifest and late prodromal HD patients receiving monthly infusions of pepinemab or placebo for 18 months in a parallel group double-blind fashion. The SIGNAL trial has used an adaptive design; in addition to measuring safety and tolerability, the study will assess numerous efficacy outcome measures including motor, cognitive, behavioral, and functional assessments; MRI brain volumetrics; and PET imaging. An early

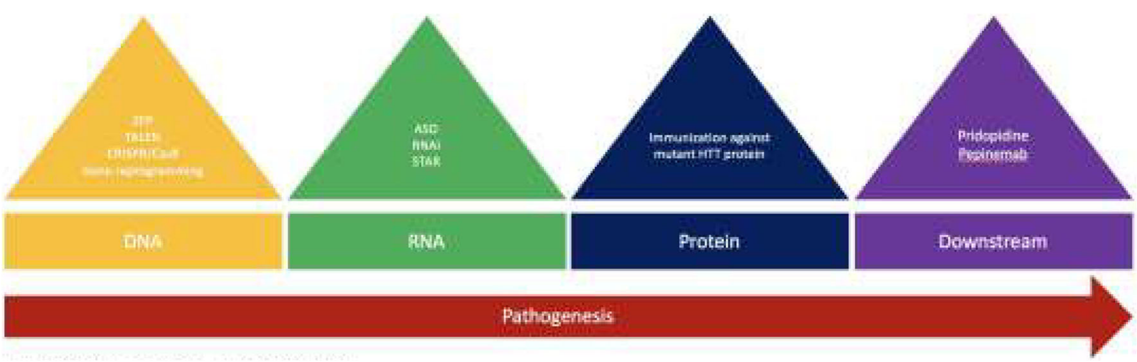

Fig. 1 Pathogenic targets of new HD therapeutics. Key: ZFP = zinc finger protein, TALEN = transcription activator-like effector nucleases, ASO = antisense oligonucleotide, RNAi = RNA interference, STAR = small-molecule therapies for alternative splicing in RNA

Table 1 New therapeutics in human clinical trials

Therapeutic	Mechanism of action	Sponsor	Clinical trial stage
Ionis-HTTrx; RG6042	Non-selective ASO binding to HTT RNA and activating RNase H-mediated degradation	Ionis Pharmaceuticals, Hoffman-LaRoche	Phase III
WVE-120101, WVE-120102	Selective ASO binding to mHTT RNA activating degradation	Wave Life Sciences	Phase I/II
AMT-130	RNAi (miRNA) against mHTT to activate RISC mediated degradation	UniQure Biopharma	Phase I/II
Pridopidine	SIG1R agonist to normalize calcium ion transport and reduce toxicity to MSNs	Prilenia	Phase II/III
Pepinemab	Anti-SEMA4D Ab to reduce neuroinflammation	Vaccinex	Phase II/III

planned interim analysis in 36 participants followed for 6 months under double-blinded conditions and an additional 5 months of open-label treatment showed no concerning safety issues and promising stabilization or reduction of decline of cortical brain atrophy and metabolism [69]. The results of the larger second cohort of the SIGNAL trial involving 265 subjects followed for 18–36 months are expected by the end of 2020.

Other New Therapeutic Approaches

Gene therapy conversion is a unique technique that is being developed in preclinical stages for application in HD. In vivo cell conversion technology reprograms adult endogenous glial cells into neurons, which avoids external transplantation and potential immunorejection [71, 72]. Studies have shown successful reprogramming of adult glial cells into functional neurons in astrocytes, NG2 cells, and mouse and monkey brains [73–75]. In vitro studies have shown successful reprogramming of fibroblast cells into medium spiny neurons [76]. In vivo studies have been published recently and show successful reprogramming of adult striatal astrocytes into functional, GABAergic striatal neurons by co-administration of two transcription factors, NeuroD1 and Dlx2, in two HD transgenic mouse models, R6/2 and YAC128 [77]. These reprogrammed neurons show similar electrophysiological properties to preexisting neurons, and these reprogrammed mouse models show partial rescue of motor functional deficits and increased survival [77••].

Another novel approach includes active and passive immunization against mutant HTT protein. Preclinical studies in HD mouse models have shown active immunization via introduction of an immunogenic short peptide that generates host B cell–mediated antigen-specific antibodies targeting exon1 of mutant HTT protein, which further downregulates aberrant neuroinflammatory and cell death pathways [78]. Other preclinical studies have designed antibody fragments directed specifically at a region in the N-terminus of the mutant HTT protein, to prevent protein misfolding. Studies in HD mouse models have shown that delivery of these therapeutic antibody fragments, via AAV vector directly into the striatum, can reduce mutant HTT aggregates [79].

As many of the therapies discussed here require invasive administration, via intraparenychymal or intrathecal delivery, there are ongoing studies examining the application of orally bioavailable small-molecule therapies for alternative splicing in RNA (STAR) technology in Huntington's disease [80]. This new technology aims to develop small molecules that target splicing modifiers in RNA structures and harness these modifiers to correct mutant, pathogenic RNA. This approach has been studied in

Table 2 New therapeutics in preclinical stages

Potential therapeutic	Mechanism of action	Preclinical studies
AAV1 delivered anti-mHTT miRNA	RNAi	Transgenic mouse model, safety in non-human primates
ZFPs	Repression of transcription via direct DNA binding	Transgenic mouse model
TALENs	Repression of transcription via direct DNA binding	HD patient–derived fibroblasts
CRISPR/Cas9	DNA cleavage	HD patient–derived fibroblasts, transgenic HD mouse model
Small-molecule modulators/ transcription factors	Downregulate HTT transcription	Transgenic mouse models
ASOs promoting exon 12 skipping	Omit caspase cleavage sites encoded in exon 12	Transgenic mouse models
Gene reprogramming	Reprogram endogenous adult glial cells into functional striatal cells	Transgenic mouse models
Immunization against mutant HTT protein	Generate immunogenicity against mHTT protein	Transgenic mouse models

changing the alternative splicing of SMN2 pre-mRNA in spinal muscular atrophy (SMA) and is now being applied to Huntington's disease and amyotrophic lateral sclerosis [81].

Conclusion

While the gene mutation underlying Huntington's disease has long been known, the pathogenesis from mutant gene to aberrant aggregation, neurotoxicity, metabolic dysfunction, and neuroimmunological dysfunction is complex and not fully understood. We have reviewed new, potential disease-modifying treatments that are targeted at various known pathogenic stages, from gene to RNA to protein pathways (Fig. 1). Several of these therapeutics are already being investigated in human clinical trials, and others show promising preclinical, in vivo data (Tables 1 and 2). The ultimate goal of these new therapies is to improve survival, function, and quality of life, and potentially cure Huntington's disease. Gene therapies show great promise in correcting or muting the underlying abnormal trinucleotide expansion at the DNA level, which would theoretically prevent all downstream aberrant pathways. Therapies directed at the RNA level are also promising in early pathogenic intervention to prevent activation of downstream mutant HTT toxicity. Therapeutic limitations common to those targeting DNA and RNA levels include invasive administration (often requiring direct intraparenychmal or intrathecal delivery), as well as potential off-target effects, with inadvertent downregulation of non-HD-related genes or transcripts. Therapies targeted at important downstream pathways include those reducing MSN atrophy and neuroinflammation. Other novel techniques in preclinical development include using endogenous, adult glial cells to regenerate striatal neurons and immunization against mutant HTT protein. These therapies may be especially significant in application to patients with advanced disease where therapy targeted at DNA or RNA levels may not reverse prior neurotoxicity. Together, these exciting and novel therapeutic strategies have raised hope that disease-modifying therapies for Huntington's disease may soon become a reality.

Compliance with Ethical Standards

Conflict of Interest Ling Pan declares that she has no conflict of interest. Andrew Feigin has consulted for NeuExcell Therapeutics, Voyager Therapeutics and Stealth BioTherapeutics. He has received grant support from Vaccinex, and Prilenia Therapeutics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human participants or animals performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Pringsheim T, Wiltshire K, Day L, Dykeman J, Steeves T, Jette N. The incidence and prevalence of Huntington's disease: a systematic review and meta-analysis. Mov Disord. 2012;27(9):1083–91. https://doi.org/10.1002/mds.25075.
2. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell. 1993;72(6):971–83. https://doi.org/10.1016/0092-8674(93)90585-e.
3. Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell. 1996;87(3):493–506. https://doi.org/10.1016/s0092-8674(00)81369-0.
4. Davies SW, Turmaine M, Cozens BA, DiFiglia M, Sharp AH, Ross CA, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell. 1997;90(3):537–48. https://doi.org/10.1016/s0092-8674(00)80513-9.
5. DiFiglia M, Sapp E, Chase KO, Davies SW, Bates GP, Vonsattel JP, et al. Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science. 1997;277(5334):1990–3. https://doi.org/10.1126/science.277.5334.1990.
6. Cha JH, Kosinski CM, Kerner JA, Alsdorf SA, Mangiarini L, Davies SW, et al. Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human Huntington disease gene. Proc Natl Acad Sci U S A. 1998;95(11):6480–5. https://doi.org/10.1073/pnas.95.11.6480.
7. Caron NS, Dorsey ER, Hayden MR. Therapeutic approaches to Huntington disease: from the bench to the clinic. Nat Rev Drug Discov. 2018;17(10):729–50. https://doi.org/10.1038/nrd.2018.133.
8. Huntington Study G. Tetrabenazine as antichorea therapy in Huntington disease: a randomized controlled trial. Neurology. 2006;66(3):366–72. https://doi.org/10.1212/01.wnl.0000198586.85250.13.
9. Huntington Study G, Frank S, Testa CM, Stamler D, Kayson E, Davis C, et al. Effect of deutetrabenazine on chorea among patients with Huntington disease: a randomized clinical trial. JAMA. 2016;316(1):40–50. https://doi.org/10.1001/jama.2016.8655.
10. Stahl CM, Feigin A. Medical, surgical, and genetic treatment of Huntington disease. Neurol Clin. 2020;38(2):367–78. https://doi.org/10.1016/j.ncl.2020.01.010.
11. Bates G. Huntingtin aggregation and toxicity in Huntington's disease. Lancet. 2003;361(9369):1642–4. https://doi.org/10.1016/S0140-6736(03)13304-1.
12. Yamamoto A, Lucas JJ, Hen R. Reversal of neuropathology and motor dysfunction in a conditional model of Huntington's disease. Cell. 2000;101(1):57–66. https://doi.org/10.1016/S0092-8674(00)80623-6.
13. Wang N, Gray M, Lu XH, Cantle JP, Holley SM, Greiner E, et al. Neuronal targets for reducing mutant huntingtin expression to ameliorate disease in a mouse model of Huntington's disease. Nat Med. 2014;20(5):536–41. https://doi.org/10.1038/nm.3514.

14. Skotte NH, Southwell AL, Ostergaard ME, Carroll JB, Warby SC, Doty CN, et al. Allele-specific suppression of mutant huntingtin using antisense oligonucleotides: providing a therapeutic option for all Huntington disease patients. PLoS One. 2014;9(9): e107434. https://doi.org/10.1371/journal.pone.0107434.
15. Kay C, Collins JA, Skotte NH, Southwell AL, Warby SC, Caron NS, et al. Huntingtin haplotypes provide prioritized target panels for allele-specific silencing in Huntington disease patients of European ancestry. Mol Ther. 2015;23(11):1759–71. https://doi.org/10.1038/mt.2015.128.
16. Leavitt BR, Kordasiewicz HB, Schobel SA. Huntingtin-lowering therapies for Huntington disease: a review of the evidence of potential benefits and risks. JAMA Neurol. 2020;77:764–72. https://doi.org/10.1001/jamaneurol.2020.0299.
17.•• Tabrizi SJ, Leavitt BR, Landwehrmeyer GB, Wild EJ, Saft C, Barker RA, et al. Targeting huntingtin expression in patients with Huntington's disease. N Engl J Med. 2019;380(24):2307–16. https://doi.org/10.1056/NEJMoa1900907 **Intrathecal ASO treatment that has demonstrated initial safety in humans and promising reduction of mHTT levels in CSF leading to phase III study initiation**.
18. Sciences WL. Wave Life Sciences reports fourth quarter and full year 2019 financial results and provides business update https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-reports-fourth-quarter-and-full-year-20192020. p. 1–2.
19. Rodrigues FB, Wild EJ. Huntington's disease clinical trials corner: March 2020. J Huntingtons Dis. 2020;9:185–97. https://doi.org/10.3233/JHD-200002.
20. Boudreau RL, McBride JL, Martins I, Shen S, Xing Y, Carter BJ, et al. Nonallele-specific silencing of mutant and wild-type huntingtin demonstrates therapeutic efficacy in Huntington's disease mice. Mol Ther. 2009;17(6):1053–63. https://doi.org/10.1038/mt.2009.17.
21. Stanek LM, Sardi SP, Mastis B, Richards AR, Treleaven CM, Taksir T, et al. Silencing mutant huntingtin by adeno-associated virus-mediated RNA interference ameliorates disease manifestations in the YAC128 mouse model of Huntington's disease. Hum Gene Ther. 2014;25(5):461–74. https://doi.org/10.1089/hum.2013.200.
22.• Pfister EL, DiNardo N, Mondo E, Borel F, Conroy F, Fraser C, et al. Artificial miRNAs reduce human mutant huntingtin throughout the striatum in a transgenic sheep model of Huntington's disease. Hum Gene Ther. 2018;29(6):663–73. https://doi.org/10.1089/hum.2017.199 **Preclinical study that helped to initiate the human clinical trial for miRNA therapy**.
23. Dufour BD, Smith CA, Clark RL, Walker TR, McBride JL. Intrajugular vein delivery of AAV9-RNAi prevents neuropathological changes and weight loss in Huntington's disease mice. Mol Ther. 2014;22(4):797–810. https://doi.org/10.1038/mt.2013.289.
24. Hordeaux J, Wang Q, Katz N, Buza EL, Bell P, Wilson JM. The neurotropic properties of AAV-PHP.B are limited to C57BL/6J mice. Mol Ther. 2018;26(3):664–8. https://doi.org/10.1016/j.ymthe.2018.01.018.
25. Matsuzaki Y, Konno A, Mochizuki R, Shinohara Y, Nitta K, Okada Y et al. Intravenous administration of the adeno-associated virus-PHP.B capsid fails to upregulate transduction efficiency in the marmoset brain. Neurosci Lett. 2018;665:182–8. https://doi.org/10.1016/j.neulet.2017.11.049.
26. McBride JL, Pitzer MR, Boudreau RL, Dufour B, Hobbs T, Ojeda SR, et al. Preclinical safety of RNAi-mediated HTT suppression in the rhesus macaque as a potential therapy for Huntington's disease. Mol Ther. 2011;19(12):2152–62. https://doi.org/10.1038/mt.2011.219.
27. Fan B, Chen, F, Jianyu, S, Nilesh, P, Tyson, K, Bittner, K, Bales, K, Khwaja, O, Carter, T, Sah, D, Pengcheng, Z. . Phenotypic benefit of intrastriatal administration of the AAV gene therapy VY-HTT01 in the YAC128 mouse model of Huntington's disease In: Therapy ASoGaC, editor. ASGCT 2020 April 28, 2020; Virtual https://www.asgct.org/global/documents/asgct20_abstracts_may8?_zs=S2i4b&_zl=U9052: Molecular Therapy; 2020. p. 95-.
28. Zhou P, Carroll, J, Chen, F, Thompson, J, Aubin, J, Christensen E, Liu, L, Nguyen, T, Scheel, M, Pechan, P, Kells, A, Gamba-Vitalo, C, Hersch, S, Hou, J, Carter, T, Sah, D Robust Huntingtin knockdown in cortex and putamen in large mammals using a novel dosing paradigm with VY-HTT01, an AAV gene therapy targeting Huntington for the treatment of Huntington's disease. In: therapy ESoGaC, editor. Changing the face of modern medicine: stem cell and gene therapy November 2018. https://www.esgct.eu/home/Previous Congresses/2018_Lausanne/2018_Lausanne_abstracts.pdf: human gene therapy 2018. p. 83-.
29. Tabrizi SJ, Ghosh R, Leavitt BR. Huntingtin lowering strategies for disease modification in Huntington's disease. Neuron. 2019;101(5):801–19. https://doi.org/10.1016/j.neuron.2019.01.039.
30. Mittelman D, Moye C, Morton J, Sykoudis K, Lin Y, Carroll D, et al. Zinc-finger directed double-strand breaks within CAG repeat tracts promote repeat instability in human cells. Proc Natl Acad Sci U S A. 2009;106(24):9607–12. https://doi.org/10.1073/pnas.0902420106.
31. Garriga-Canut M, Agustin-Pavon C, Herrmann F, Sanchez A, Dierssen M, Fillat C, et al. Synthetic zinc finger repressors reduce mutant huntingtin expression in the brain of R6/2 mice. Proc Natl Acad Sci U S A. 2012;109(45):E3136–45. https://doi.org/10.1073/pnas.1206506109.
32. Fink KD, Deng P, Gutierrez J, Anderson JS, Torrest A, Komarla A, et al. Allele-specific reduction of the mutant huntingtin allele using transcription activator-like effectors in human Huntington's disease fibroblasts. Cell Transplant. 2016;25(4):677–86. https://doi.org/10.3727/096368916X690863.
33.•• Dabrowska M, Juzwa W, Krzyzosiak WJ, Olejniczak M. Precise excision of the CAG tract from the huntingtin gene by Cas9 nickases. Front Neurosci. 2018;12:75. https://doi.org/10.3389/fnins.2018.00075 **Preclinical study demonstarting application of CRISPR/Cas9 DNA editing technique to HTT gene**.
34.•• Yang S, Chang R, Yang H, Zhao T, Hong Y, Kong HE, et al. CRISPR/Cas9-mediated gene editing ameliorates neurotoxicity in mouse model of Huntington's disease. J Clin Invest. 2017;127(7):2719–24. https://doi.org/10.1172/JCI92087 **Preclinical study applycing CRISPR/Cas9 DNA editing technology to HD mouse model**.
35. Muhlback A, editor. Report from the 14th Huntington's disease therapeutics conference Hungtington's disease therapeutics conference 2019; Palm Springs, USA eurohuntington.org/2019/04/01/report-from-the-14th-huntingtons-disease-therapeutics-conference/2019.
36. Liu CR, Chang CR, Chern Y, Wang TH, Hsieh WC, Shen WC, et al. Spt4 is selectively required for transcription of extended trinucleotide repeats. Cell. 2012;148(4):690–701. https://doi.org/10.1016/j.cell.2011.12.032.
37.•• Cheng HM, Chern Y, Chen IH, Liu CR, Li SH, Chun SJ et al. Effects on murine behavior and lifespan of selectively decreasing expression of mutant huntingtin allele by supt4h knockdown. PLoS Genet. 2015;11(3):e1005043. https://doi.org/10.1371/journal.pgen.1005043. **Preclinical study demonstrating application of small molecule modulators directed towards transcription factors in downregulating mutant huntingtin allele**.

38. Graham RK, Deng Y, Slow EJ, Haigh B, Bissada N, Lu G, et al. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. Cell. 2006;125(6):1179–91. https://doi.org/10.1016/j.cell.2006.04.026.
39. Gafni J, Hermel E, Young JE, Wellington CL, Hayden MR, Ellerby LM. Inhibition of calpain cleavage of huntingtin reduces toxicity: accumulation of calpain/caspase fragments in the nucleus. J Biol Chem. 2004;279(19):20211–20. https://doi.org/10.1074/jbc.M401267200.
40. Pouladi MA, Graham RK, Karasinska JM, Xie Y, Santos RD, Petersen A, et al. Prevention of depressive behaviour in the YAC128 mouse model of Huntington disease by mutation at residue 586 of huntingtin. Brain. 2009;132(Pt 4):919–32. https://doi.org/10.1093/brain/awp006.
41. Casaca-Carreira J, Toonen LJA, Evers MM, Jahanshahi A, van-Roon-Mom WMC, Temel Y. In vivo proof-of-concept of removal of the huntingtin caspase cleavage motif-encoding exon 12 approach in the YAC128 mouse model of Huntington's disease. Biomed Pharmacother. 2016;84:93–6. https://doi.org/10.1016/j.biopha.2016.09.007.
42. Vonsattel JP, DiFiglia M. Huntington disease. J Neuropathol Exp Neurol. 1998;57(5):369–84. https://doi.org/10.1097/00005072-199805000-00001.
43. Vonsattel JP, Myers RH, Stevens TJ, Ferrante RJ, Bird ED, Richardson EP Jr. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol. 1985;44(6):559–77. https://doi.org/10.1097/00005072-198511000-00003.
44. Tabrizi SJ, Reilmann R, Roos RA, Durr A, Leavitt B, Owen G, Jones R, Johnson H, Craufurd D, Hicks SL, Kennard C, Landwehrmeyer B, Stout JC, Borowsky B, Scahill RI, Frost C, Langbehn DR, TRACK-HD investigators. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol 2012;11(1):42–53. https://doi.org/10.1016/S1474-4422(11)70263-0.
45. Gerfen CR, Engber TM, Mahan LC, Susel Z, Chase TN, Monsma FJ Jr, et al. D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. Science. 1990;250(4986):1429–32. https://doi.org/10.1126/science.2147780.
46. Deng YP, Albin RL, Penney JB, Young AB, Anderson KD, Reiner A. Differential loss of striatal projection systems in Huntington's disease: a quantitative immunohistochemical study. J Chem Neuroanat. 2004;27(3):143–64. https://doi.org/10.1016/j.jchemneu.2004.02.005.
47. Ghosh R, Tabrizi SJ. Clinical features of Huntington's disease. Adv Exp Med Biol. 2018;1049:1–28. https://doi.org/10.1007/978-3-319-71779-1_1.
48. Fatoba O, Ohtake Y, Itokazu T, Yamashita T. Immunotherapies in Huntington's disease and alpha-Synucleinopathies. Front Immunol. 2020;11:337. https://doi.org/10.3389/fimmu.2020.00337.
49. Sapp E, Kegel KB, Aronin N, Hashikawa T, Uchiyama Y, Tohyama K, et al. Early and progressive accumulation of reactive microglia in the Huntington disease brain. J Neuropathol Exp Neurol. 2001;60(2):161–72. https://doi.org/10.1093/jnen/60.2.161.
50. Pavese N, Gerhard A, Tai YF, Ho AK, Turkheimer F, Barker RA, et al. Microglial activation correlates with severity in Huntington disease: a clinical and PET study. Neurology. 2006;66(11):1638–43. https://doi.org/10.1212/01.wnl.0000222734.56412.17.
51. Bjorkqvist M, Wild EJ, Thiele J, Silvestroni A, Andre R, Lahiri N, et al. A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. J Exp Med. 2008;205(8):1869–77. https://doi.org/10.1084/jem.20080178.
52. Tai YF, Pavese N, Gerhard A, Tabrizi SJ, Barker RA, Brooks DJ, et al. Microglial activation in presymptomatic Huntington's disease gene carriers. Brain. 2007;130(Pt 7):1759–66. https://doi.org/10.1093/brain/awm044.
53. Rocha NP, Ribeiro FM, Furr-Stimming E, Teixeira AL. Neuroimmunology of Huntington's disease: revisiting evidence from human studies. Mediat Inflamm. 2016;2016:8653132–10. https://doi.org/10.1155/2016/8653132.
54. Rizzuto R, Duchen MR, Pozzan T. Flirting in little space: the ER/mitochondria Ca2+ liaison. Sci STKE. 2004;2004(215):re1. https://doi.org/10.1126/stke.2152004re1.
55. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. Cell. 2007;131(3):596–610. https://doi.org/10.1016/j.cell.2007.08.036.
56. Tang TS, Slow E, Lupu V, Stavrovskaya IG, Sugimori M, Llinas R, et al. Disturbed Ca2+ signaling and apoptosis of medium spiny neurons in Huntington's disease. Proc Natl Acad Sci U S A. 2005;102(7):2602–7. https://doi.org/10.1073/pnas.0409402102.
57. Tang TS, Tu H, Chan EY, Maximov A, Wang Z, Wellington CL, et al. Huntingtin and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol-(1,4,5) triphosphate receptor type 1. Neuron. 2003;39(2):227–39. https://doi.org/10.1016/s0896-6273(03)00366-0.
58. Garcia-Miralles M, Geva M, Tan JY, Yusof N, Cha Y, Kusko R et al. Early pridopidine treatment improves behavioral and transcriptional deficits in YAC128 Huntington disease mice. JCI Insight. 2017;2(23). https://doi.org/10.1172/jci.insight.95665.
59. Ryskamp D, Wu J, Geva M, Kusko R, Grossman I, Hayden M et al. The sigma-1 receptor mediates the beneficial effects of pridopidine in a mouse model of Huntington disease. Neurobiol Dis. 2017;97(Pt A):46–59. https://doi.org/10.1016/j.nbd.2016.10.006.
60. Squitieri F, Di Pardo A, Favellato M, Amico E, Maglione V, Frati L. Pridopidine, a dopamine stabilizer, improves motor performance and shows neuroprotective effects in Huntington disease R6/2 mouse model. J Cell Mol Med. 2015;19(11):2540–8. https://doi.org/10.1111/jcmm.12604.
61. Huntington Study Group HI. A randomized, double-blind, placebo-controlled trial of pridopidine in Huntington's disease. Mov Disord. 2013;28(10):1407–15. https://doi.org/10.1002/mds.25362.
62. de Yebenes JG, Landwehrmeyer B, Squitieri F, Reilmann R, Rosser A, Barker RA, Saft C, Magnet MK, Sword A, Rembratt A, Tedroff J, MermaiHD study investigators. Pridopidine for the treatment of motor function in patients with Huntington's disease (MermaiHD): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2011;10(12):1049–1057. https://doi.org/10.1016/S1474-4422(11)70233-2.
63.•• Reilmann R, McGarry A, Grachev ID, Savola JM, Borowsky B, Eyal E et al. Safety and efficacy of pridopidine in patients with Huntington's disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study. Lancet Neurol. 2019;18(2):165–76. https://doi.org/10.1016/S1474-4422(18)30391-0. **Initial results from phase II study of pridopidine suggesting improvement of motor scores and dystonia in early stage participants**.
64.•• Kieburtz Kea. Efficacy, safety, and tolerability of pridopidine in Huntington disease (HD): results from the phase II, double-blind, placebo-controlled, dose-ranging study, Pride-HD [abstract]. . Mov Disord. 2017;32 (suppl. 2). **Important post-hoc analysis from phase II study of pridopidine showing benefit in TFC scores**.
65. Kumanogoh A, Watanabe C, Lee I, Wang X, Shi W, Araki H, et al. Identification of CD72 as a lymphocyte receptor for the class IV semaphorin CD100: a novel mechanism for regulating B cell signaling. Immunity. 2000;13(5):621–31. https://doi.org/10.1016/s1074-7613(00)00062-5.
66. Okuno T, Nakatsuji Y, Moriya M, Takamatsu H, Nojima S, Takegahara N, et al. Roles of Sema4D-plexin-B1 interactions in the central nervous system for pathogenesis of experimental

autoimmune encephalomyelitis. J Immunol. 2010;184(3):1499–506. https://doi.org/10.4049/jimmunol.0903302.
67. Southwell AL, Franciosi S, Villanueva EB, Xie Y, Winter LA, Veeraraghavan J, et al. Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of Huntington disease. Neurobiol Dis. 2015;76:46–56. https://doi.org/10.1016/j.nbd.2015.01.002.
68. LaGanke C, Samkoff L, Edwards K, Jung Henson L, Repovic P, Lynch S, et al. Safety/tolerability of the anti-semaphorin 4D antibody VX15/2503 in a randomized phase 1 trial. Neurol Neuroimmunol Neuroinflamm. 2017;4(4):e367. https://doi.org/10.1212/NXI.0000000000000367.
69. Evans E, editor. Regulation of glial cell activation and neurodegeneration by anti-semaphorin 4D antibody pepinemab, potential treatment for Alzheimer's and Huntington's disease Advances in Alzheimer's and Parkinson's therapies an AAT-AD/PD focus meeting April 2020; Vienna, Austria; https://ir.vaccinex.com/static-files/7affd508-0cbc-490d-9567-be4064b7bafc.
71. Torper O, Ottosson DR, Pereira M, Lau S, Cardoso T, Grealish S, et al. In vivo reprogramming of striatal NG2 glia into functional neurons that integrate into local host circuitry. Cell Rep. 2015;12(3):474–81. https://doi.org/10.1016/j.celrep.2015.06.040.
72. Barker RA, Gotz M, Parmar M. New approaches for brain repair-from rescue to reprogramming. Nature. 2018;557(7705):329–34. https://doi.org/10.1038/s41586-018-0087-1.
73. Pereira M, Birtele M, Shrigley S, Benitez JA, Hedlund E, Parmar M, et al. Direct reprogramming of resident NG2 glia into neurons with properties of fast-spiking parvalbumin-containing interneurons. Stem Cell Reports. 2017;9(3):742–51. https://doi.org/10.1016/j.stemcr.2017.07.023.
74. Niu W, Zang T, Smith DK, Vue TY, Zou Y, Bachoo R, et al. SOX2 reprograms resident astrocytes into neural progenitors in the adult brain. Stem Cell Reports. 2015;4(5):780–94. https://doi.org/10.1016/j.stemcr.2015.03.006.
75. Ge L-J, Yang, F-H., Chen, N-H., Jiang, M., Wang, J-H., Hu, X-T., Chen, G. . In vivo neuroregeneration to treat ischemic stroke in adult non-human primate brains throught NeuroD1 AAV-based gene therapy. bioRxiv. 2019. https://doi.org/10.1101/816066.
76. Victor MB, Richner M, Hermanstyne TO, Ransdell JL, Sobieski C, Deng PY, et al. Generation of human striatal neurons by microRNA-dependent direct conversion of fibroblasts. Neuron. 2014;84(2):311–23. https://doi.org/10.1016/j.neuron.2014.10.016.
77.•• Wu Z, Parry M, Hou XY, Liu MH, Wang H, Cain R et al. Gene therapy conversion of striatal astrocytes into GABAergic neurons in mouse models of Huntington's disease. Nat Commun. 2020;11(1):1105. https://doi.org/10.1038/s41467-020-14855-3. **Preclinical studies showing potential to reprogram glial cells into functional striatal cells in HD mouse models**.
78. Ramsingh AI, Manley K, Rong Y, Reilly A, Messer A. Transcriptional dysregulation of inflammatory/immune pathways after active vaccination against Huntington's disease. Hum Mol Genet. 2015;24(21):6186–97. https://doi.org/10.1093/hmg/ddv335.
79. Butler DC, Messer A. Bifunctional anti-huntingtin proteasome-directed intrabodies mediate efficient degradation of mutant huntingtin exon 1 protein fragments. PLoS One. 2011;6(12):e29199. https://doi.org/10.1371/journal.pone.0029199.
80. Iqra Mumal M. Skyhawk, Celgene partner to develop small molecule treatments for Huntington's, other neurological diseases Huntington's disease news https://huntingtonsdiseasenews.com/2018/07/05/huntingtons-disease-other-neurological-disorders-target-skyhawk-therapeutics-celgene-partnership/. 2018.
81. Sivaramakrishnan M, McCarthy KD, Campagne S, Huber S, Meier S, Augustin A, et al. Binding to SMN2 pre-mRNA-protein complex elicits specificity for small molecule splicing modifiers. Nat Commun. 2017;8(1):1476. https://doi.org/10.1038/s41467-017-01559-4.