

# Orphan drugs in development for Huntington's disease: challenges and progress

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**Abstract:** Huntington's disease is a monogenic disorder encompassing a variable phenotype with progressive cognitive, psychiatric, and movement disorders. Knowledge of the mechanisms involved in this disorder has made substantial advances since the discovery of the gene mutation. The dynamic mutation is the expansion of a CAG (cytosine-adenine-guanine) repeat in the huntingtin (*HTT*) gene, which is transcribed into an abnormal protein with an elongated polyglutamine tract. Polyglutamine HTT accumulates and is changed in its function in multifaceted ways related to the numerous roles of the normal protein. The protein is expressed in numerous areas of the brain and also in other organs. The major brain region involved in the disease process is the striatum, but it is clear that other systems are involved as well. This accumulated knowledge has now led to the development of treatment strategies based on specific molecular pathways for symptomatic and disease course-modifying treatment. The most proximal way to handle the disturbed protein is to hinder the gene transcription, translation, and/or to increase protein clearance. Other mechanisms now being approached include modulation of energy and intracellular signaling, induction of factors potentially leading to neuroprotection, as well as modulation of glial function. Several clinical trials based on these approaches are now under way, and it is becoming clear that a future disease-modifying therapy will be a combination of several approaches harmonized with symptomatic treatments. In this review, some of the most promising and advanced strategies to develop novel treatments in Huntington's disease are examined.

**Keywords:** Huntington's disease, symptomatic treatment, disease-modifying therapy

## Introduction

Huntington's disease (HD) is characterized by a complex phenotype including motor, cognitive, and psychiatric symptoms and signs starting at different ages and gradually evolving over the years until death after 15–25 years.<sup>1,2</sup> The mutation of this autosomal-dominant inherited disorder is fully penetrant, and HD can be diagnosed well in advance of any symptom, as opposed to other, more frequent degenerative disorders of the brain, including Parkinson's and Alzheimer's disease. There is a long presymptomatic phase, during which opportunities for a disease-modifying treatment might be tested and applied, since the molecular diagnosis allows a clear inclusion of people who will develop the disease. No neuroprotective treatment is yet available, and drugs used now treat symptoms only. However, comprehensive care, of which drug treatment is only a part, can be suggested to modify the course of the disorder, specifically through avoiding further complications. A tremendous amount of data on the multifaceted pathophysiology of the brain and systemic disorder included in HD have been accumulated in the last few years.

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The increased numbers of a CAG (cytosine-adenine-guanine)-triplet repeat in exon 1 of the huntingtin (*HTT*) gene located on chromosome 4p16.3<sup>3</sup> leads after translation to a polyglutamine elongation at the C-terminal of the protein. The polyglutamine tract leads to HTT accumulation in the cell, due to complex mechanisms of protein aggregation through progressive fibril formation.<sup>4</sup> Furthermore, HTT mutation impairs a number of cellular functions.<sup>5</sup> These include gene transcription and intracellular and synaptic signaling mechanisms. Furthermore, cellular functions like energy metabolism, mitochondrial function, intracellular protein trafficking and dynamic axonal transport mechanisms, and endocytic and vesicular trafficking changes are involved as well. The major region involved in the disease process is the striatum, but other brain areas are involved as well, including the cortex and the hypothalamus. Furthermore, it is increasingly recognized that changes occur in other organs as well. All these molecular mechanisms and systemic involvements represent potential targets for disease-modifying strategies. Furthermore, HTT is involved in a large number of interactions with other proteins and pathways,<sup>6</sup> and polyglutamine expansion may modify them.<sup>7</sup> This contributes to the complexity of molecular events involved in the disease, but also to the number of potential targets.

## Huntington's disease: a complex phenotype

Typically, early HD is characterized by the occurrence of subtle cognitive and behavioral changes with involuntary, hyperkinetic, choreatic movements at around 40 years old, but there are large variations in the phenotype and time course, including the sequence of symptom development. Variation of age at onset, usually defined as age at the appearance of clear motor signs, is mainly dependent upon the number of triplet repeats, with a negative correlation and younger age at onset in cases with higher numbers. The course is relentlessly progressive, but with fluctuations, particularly observed for the behavioral symptoms. In the face of such a variation, the importance of using appropriate assessment methods and meaningful end points in clinical trials cannot be stressed enough, as is also the case for symptomatic management.<sup>8</sup>

Trials can be grouped into symptomatic and disease-modifying treatments; however, the boundary between these is not always absolute. Purely symptomatic modalities may change the course of the disease, eg, by avoiding complications like social isolation. They may also modify adaptive plastic synaptic changes that secondarily participate in the

disease process. On the other hand, treatment targeted at long-term disease-course modification may also have an acute symptomatic effect. Issues in clinical trials include the proper choice of age at onset assessment and biomarkers used as end points. Typically, the age at occurrence of first motor symptoms and signs has been considered as defining the age at disease onset. However, experience shows that cognitive and behavioral changes may occur before motor impairment, which is also often subtle during the phenocconversion period. A better method is to capture the history of motor, behavior (depression, irritability, apathy, aggressive behavior, obsession, and psychosis), and cognitive impairment in an open and unbiased way, as is done within the European Huntington's Disease Network Registry (<http://www.euro-hd.net>) and the global Enroll-HD (<http://studies.enroll-hd.org>) studies.

Progress has been made in informing the choice of biomarkers, which has to be tailored to the respective pathway targeted by the intervention under scrutiny. Track-HD, an intensive, 3-year study, has examined of a cohort of HD gene carriers in a premanifest and in an early stage of the disease.<sup>9-11</sup> Assessment has included a complex battery, with cognitive, quantitative motor, oculomotor, and neuropsychiatric measures, as well as imaging methods. Magnetic resonance imaging assessments, including whole-brain atrophy, ventricular expansion, caudate atrophy, putamen atrophy, and white-matter atrophy, have turned out to be valuable biomarkers both in the presymptomatic and in the early manifest stages, with cognitive tests, including the symbol digit modality test, the Stroop word-reading and the emotion-recognition tests providing additional information in a subgroup.<sup>11</sup>

## Gene therapy

In order to decrease the expression of the abnormal, long-allele-bearing *HTT* gene, different types of strategies have been developed. They include the use of interfering ribonucleic acid (RNA) molecules, antisense oligonucleotides (ASOs), and proteins modulating the transcription process. They may be grouped according to specificity, recognizing the elongated allele only in a selective (allele-specific) or nonselective (allele-nonspecific) way. A decrease in HTT expression improves symptoms and prolongs survival in HD mouse models.<sup>12,13</sup>

ASOs, specifically targeted HTT messenger RNA (mRNA),<sup>14</sup> induce degradation by RNase activity and can be modified to make them resistant to exonuclease cleavage, which improves their stability. After injection in the brain of

HD animal models, ASOs decrease HTT mRNA levels in the striatum without morphological change, followed after a time lag by a return to previous mutant HTT mRNA levels.<sup>15</sup> ASO therapies are in the process of development in other neurodegenerative disorders, and have reached clinical trials in some instances. For example, one such trial that has been started to examine safety, tolerability, and activity of an ASO treatment is presently undergoing in amyotrophic lateral sclerosis caused by *SOD1* gene mutations (<http://clinicaltrials.gov/show/NCT01041222>). There has been a Phase I study in children with spinal muscular atrophy with an ASO targeting SMN2, and the treatment was well tolerated; in an autopsy case, cortical and spinal neuron targeting were reported. Phase II and III trials are planned in spinal muscular atrophy and also in amyotrophic lateral sclerosis. The HD study uses a similar chemical ASO composition. A safety study using ASOs, applied by repetitive monthly lumbar administration with dose escalation in HD patients, is planned in 2015. This will include a large array of detailed cerebrospinal fluid studies, including immunological and chemical assessments and also some exploratory end points.

Small interfering RNA (siRNA) or micro-interfering RNA bind to the abnormal transcript, which undergoes degradation by the RNA-induced silencing complex with a consecutive decrease in mutated protein, and this approach has been

found to improve the phenotype in animal models.<sup>16</sup> siRNA may be designed specifically to target the mutant allele in a selective way, with conservation of normal wild-type HTT expression.<sup>17</sup> A general proof of concept for a siRNA therapy has been delivered in healthy volunteers inoculated with respiratory syncytial virus, in whom it has demonstrated its expected antiviral activity.<sup>18</sup> The molecule may be packaged into modified adenoviruses acting as a vector, and stereotactic injections of such constructs have been found to be safe in primates for 6 months.<sup>19</sup> This treatment is followed by a significant decrease in HTT mRNA compared with controls. A Phase I study using continuous, pump system-mediated intracerebral application of an RNA-interference therapeutic agent had been announced,<sup>20</sup> but its later retraction demonstrates the difficult path along the way of such strategies. The chemical properties of the compounds also play a role, and their modification may improve efficacy and tissue spread.<sup>21</sup> Promising, however, is the authorization of gene-silencing compounds for the treatment of cytomegalovirus and of familial hypercholesterolemia, with more trials running and in preparation for other diseases.<sup>22</sup>

A third potential way to decrease HTT mRNA is the use of factors that could inhibit transcription, eg, zinc-finger protein (ZFP).<sup>23</sup> Long ZFPs have been prepared to bind CAG repeats in a selective way and to be expressed in an HD cell-line

**Table I** Major planned and ongoing clinical trials in Huntington's disease

Target	Compound	Design	Status
mRNA lowering	Allele-nonspecific ASOs	Intrathecal injection, safety study	Planned for 2015
	Allele-specific ASOs	Intrastriatal injection	Preclinical
	Allele-nonspecific siRNA	Intrastriatal convection-enhanced delivery	Preclinical
	Allele-nonspecific siRNA	AAV delivery, intrastriatal injection	Preclinical
	Allele-specific zinc-finger protein transcriptional repressor	AAV delivery, intrastriatal injection	Preclinical
Inhibition of aggregation	Calpastatin, nicardipine, minoxidil, trehalose	Mouse	Preclinical
	Phosphodiesterase 10A inhibition	PF-0254920	Ongoing
KMO inhibition	OMS643762	Randomized double-blind study on efficacy and tolerability (motor score), Phase II	Ongoing
	CHDI-340246	Randomized, placebo-controlled on safety and tolerability, Phase II	Ongoing
Protein-conformation modification	PBT2	Mouse	Preclinical
	Laquinimod	Randomized, double-blind safety and tolerability, Phase II	Results publication expected
Immunomodulation	Laquinimod	Randomized, double-blind, placebo-controlled, efficacy study (motor), Phase II	Ongoing
	Neuromodulation	Pridopidine	Open label, single-group assignment study to assess long-term safety, Phase II
Neuromodulation	Tetrabenazine	Prospective case-control study to compare Stroop visual interference scores	Ongoing
	SD-809 ER (related to tetrabenazine)	Randomized double-blind study on chorea	Ongoing

**Abbreviations:** mRNA, messenger ribonucleic acid; ASOs, antisense oligonucleotides; siRNA, small interfering RNA; AAV, adenoassociated viral; KMO, kynurenine monoxygenase.

model, with the effect of a decreased expression of the longer allele, and this was also achieved after striatal delivery using an adenoassociated virus system.<sup>24</sup>

There are major hurdles in the path toward *HTT* gene silencing in humans; they include finding the appropriate delivery process, choice of target and tissue volume to be included, and timing of treatment along the course of evolution. Modes of application may include stereotactic intrastriatal delivery in the form of injections or infusions, which can be combined with convection-enhancing processes or with carriers facilitating diffusion, intraventricular injections or continuous delivery with pumps, and viral vectors or other cargo systems with selective brain targeting. Of course, the major size difference between the brains of animal models used so far and the human brain represents a major challenge. Furthermore, the course of long-term effects and side effects in general also need to be better understood. However, these strategies do offer the most upstream option to target the multifaceted molecular pathophysiology of HD in a meaningful way. It is now great news that Phase I trials are on the verge of being launched (Table 1).

## Targeting the mutated protein

Following CAG-repeat expansion in the *HTT* gene, a polyglutamine tail is translated in the molecule. HTT is a complex protein involved in a number of posttranslational modifications, including acetylation, phosphorylation, SUMOylation, ubiquitination, palmitoylation, and proteolytic cleavage. This opens the potential to modulate the posttranslational intracellular handling of the molecule with the aim of decreasing levels of abnormal huntingtin,<sup>25</sup> while retaining enough of the normal protein to attend to its numerous functions. Such compounds may be easily available and with low toxicity, like polyphenol (2)-epigallocatechin-3-gallate (EGCG), a component of green tea. EGCG inhibits mutated huntingtin aggregation in vitro,<sup>26</sup> and a Phase II trial in HD is under way (<http://clinicaltrials.gov/show/NCT01357681>).

Acetylation of mutated HTT promotes its degradation, and sirtuins are involved in this posttranslational modification of the protein. Inhibition of sirtuin 1-induced deacetylation by selisistat improves a number of parameters in HD models, including cells, *Drosophila*, and mice, specifically including behavior.<sup>27</sup> A randomized, double-blind, placebo-controlled Phase IB trial examining pharmacodynamic handling of the molecule has now been run in HD patients,<sup>28</sup> followed by a safety and tolerability study.<sup>29</sup> In the latter, 144 patients were randomized to selisistat 50 or 200 mg or placebo once daily for 12 weeks. There were three adverse events in each group; the

most common were reversible liver-function test impairments. No change in the Unified Huntington's Disease Rating Scale (UHDRS) was observed. Levels of soluble mutant huntingtin in peripheral blood mononuclear cells showed a borderline increase in the selisistat arms. So far, these data have only been published in abstract form, but the modulation of HTT levels, if confirmed, is an interesting novel finding.

Chaperones may be used to improve clearance of the abnormal protein, eg, by overexpressing heat-shock proteins. Expression of a human heat-shock protein in HSJ1a in HD mice led to a significant decrease in insoluble HTT with diminished inclusion size.<sup>30</sup> This can also be achieved by the application of antibodies specifically to react with mutated huntingtin, eg, with single-chain, single-domain antibodies shown to decrease abnormal HTT in several animal models, which is followed by clinical improvement.<sup>31</sup> Another approach to decrease the HTT protein with an elongated polyglutamine tail is based on the fact that the protein accumulation is strongly influenced in vivo by the ratio of normal to elongated HTT,<sup>32</sup> and that wild-type HTT has a protective role in HD mice.<sup>33</sup> A 23-amino acid peptide within HTT, which prevents aggregation in a *Drosophila* HD model, has been delivered to HD mice by using a nanostructure-based drug-delivery system applied by buccal or anal administration.<sup>34</sup> The peptide was appropriately delivered to the brain, and histological as well as clinical parameters were improved. A recent study has demonstrated the efficacy of such an approach in *Drosophila* and mice.<sup>35</sup> This delivery mechanism is being studied in other disorders, and knowledge accumulating in those studies will be beneficial for the potential development of this concept in HD as well.

## Improving neurotransmission

Phosphodiesterase 10A (PDE10A) is a member of a large family of enzymes, which regulate intracellular signaling by hydrolyzing cyclic nucleotides. PDE10A is specifically and highly expressed in medium spiny neurons,<sup>36</sup> one of the major neuronal populations affected by the disorder, and cyclic adenosine monophosphate (cAMP) is progressively decreased in HD knock-in mice, even during the presymptomatic phase.<sup>37</sup> PDE10A inhibition leads to a restricted accumulation of cyclic guanosine monophosphate and cAMP in the striatum,<sup>38</sup> followed by an increase in phosphorylation of a number of proteins involved in signaling, eg, Glu1 subunits<sup>39</sup> and extracellular signal-regulated kinase.<sup>40</sup> Furthermore, mutated huntingtin protein interacts with CBP/CREB-binding protein,<sup>41</sup> leading to the suggestion that increased cAMP could at least partially restore this pathway.

Preclinical evidence has accumulated to suggest a potential use in humans as well. Chronic inhibition of PDE10A and PDE10A knockout leads to changes in the expression of selective genes in the striatum, including induction of the expression of genes potentially involved in neuroprotection.<sup>42</sup> Acute PDE10A inhibition is followed by a decrease in spontaneous and amphetamine-stimulated locomotor activity,<sup>43</sup> and reduces striatal excitotoxicity in a model of HD based on quinolinic acid injection.<sup>44</sup> In the R6/2 mouse model of HD, chronic inhibition of PDE10A improves striatal and cortical morphological changes, with improvement of motor function.<sup>45</sup> It also improves cognitive function, including spatial and recognition memories.<sup>46</sup> One potential issue is the fact that striatal PDE mRNA and protein levels are decreased in transgenic mice;<sup>47</sup> however, using positron emission tomography ligands, binding is still measurable in people affected with HD, albeit in much-decreased overall levels.<sup>48</sup>

Several trials are now under way to examine the potential of chronic PDE10 in people with HD. A randomized, placebo-controlled, double-blind study on the effect of different doses of PF-02545920, a drug with US Food and Drug Administration (FDA) orphan drug designation, has recently been started as a proof of concept (<http://clinicaltrials.gov/show/NCT01806896>). The trial is going to include 260 patients randomized in groups to receive two doses or placebo, and the total motor score used as a primary outcome. Secondary outcomes include occurrence of abnormal movements, global impression, suicide rate, and hematological parameters. Imaging substudies are also included. The study will last 26 weeks, and final data collection is planned for early 2016. A Phase II trial has been started aimed at enrolling about 120 patients with HD in order to compare the effect of three different doses of OMS643762, another drug that has received FDA orphan drug designation, and placebo on a battery of assessments covering motor, cognitive, and psychiatric symptoms (<http://clinicaltrials.gov/show/NCT02074410>). Treatment duration is 28 days, and the final data collection for primary outcome assessment should be completed in March 2015. Primary outcome measures include safety assessment, and secondary ones motor function, cognition, behavior, and pharmacokinetic data. Tracers measuring enzyme availability have been developed and tested for the purpose of these studies, and have even been suggested as parameters to measure the striatal effect of other therapies.

## Improving mitochondrial function

Impaired mitochondrial function is impaired in HD, as demonstrated by dysfunction of several complexes along

the electron-transport chain,<sup>49,50</sup> decrease in mitochondrial density, and morphological alteration in brains from HD patients.<sup>51</sup> Mutated HTT impairs mitochondrial function by a number of different mechanisms, including permeability transition-pore modulation, decrease of PGC $\alpha$  expression, stimulation of glutamate receptor by increased depolarization, mitochondrial fractionation, and impaired respiratory chain function.<sup>52</sup> Several therapeutic approaches have been followed based on this background.

Coenzyme Q is a lipid-soluble antioxidant molecule with membrane-stabilizing properties involved in oxidative phosphorylation. Neuroprotective effects due to improved mitochondrial function have been tested in HD, with conflicting results. Since higher doses are safe,<sup>53</sup> a study has been performed to examine their effects over a longer period of time; however, this has been stopped for futility reasons.

Olesoxime is a small cholesterol-like molecule targeting mitochondrial pores, which has been found to delay muscle denervation, glial changes, and motoneuron degeneration in animal models of motoneuron disorders.<sup>54</sup> The drug has been tested in people with amyotrophic lateral sclerosis, but did not change the course of the disorder;<sup>55</sup> however, the drug was found to be safe. Olesoxime has demonstrated restorative effects in different models of HD, which were suggested to be due to an improvement of mitochondrial membrane.<sup>56</sup> The drug has been tested in a rat model of HD and found to improve biological and clinical parameters.<sup>57</sup> Considering the positive tolerance profile found in clinical trials in other diseases, it would seem reasonable to test it in HD as well.

## Modulation of intracellular copper content

Aggregation of HTT protein to form inclusions is stimulated by the addition of copper in the culture medium of cells expressing the glutamine elongated protein, which is reversed by copper chelation.<sup>58</sup> PBT2 is a copper chelator with a structure related to clioquinol, which has been tested in Alzheimer's disease under the assumption that the prevention of  $\beta$ -amyloid aggregation after a decrease in copper binding with the protein would improve symptoms and disease progression. In a mouse HD model, PBT2 improved motor function and prolonged survival.<sup>59</sup> PBT2 has been examined in several trials in humans. The drug decreased cerebrospinal fluid amyloid in patients with Alzheimer's in a dose-dependent way.<sup>60</sup> A Phase II study has been run in patients with HD in the US and Australia, including 109 patients in the mild-to-moderate stage of the disease. In



a press release, improvement of some cognitive function was mentioned; however, peer review of the publication will be needed to judge it, and a Phase III trial is contemplated.<sup>61</sup>

## Inhibition of excitotoxicity

Quinolinic acid, which had been used to generate HD animal models prior to the establishment of genetic ones, is generated in the brain after degradation of tryptophan, mainly by kynurenine monooxygenase (KMO) in microglial cells.<sup>62</sup> Quinolinic acid and 3-hydroxykynurenine are neurotoxic, while kynurenine and kynurenic acid are neuroprotective. The increased levels of quinolinic acid in the brain of animal models and humans with HD suggests that inhibition of this pathway may lead to protection against neurotoxicity in shifting the balance to neuroprotection. Indeed, treatment of HD mice with a KMO inhibitor has led to restoration of markers of synaptic function, decrease in glial hyperactivation, and prolonged animal survival.<sup>63</sup> There has been a debate whether this effect occurs centrally or peripherally, and a peripherally acting KMO inhibitor has been reported to increase levels of the neuroprotective quinolinic acid metabolites kynurenic acid and kynurenine in the brain and cerebrospinal fluid of animals.

## Modulation of immune function

Immune function is involved in HD, and there is widespread activation of immunological markers in patients and also in asymptomatic gene carriers even long before disease onset.<sup>64</sup> These changes mirror findings in animal models of HD, and they have led to the suggestion of a parallel involvement of brain and immune mechanisms underlying the disease process. This immune activation may be mediated by a pathway involving nuclear factor  $\kappa$ B, and HTT lowering reverses immune-function impairment induced by this factor.<sup>65</sup> Laquinimod, a drug that has been developed for the treatment of multiple sclerosis, decreases nuclear factor  $\kappa$ B in astrocytes.<sup>66</sup> Laquinimod decreases relapse rate, disability, and brain atrophy in multiple sclerosis,<sup>67</sup> and there is also good evidence to suggest a decrease in brain damage.<sup>68</sup> Based on this rationale, a proposal has been made to explore the use of this drug in HD as well. The advantage of the substance is that it has been used in quite a large number of patients with multiple sclerosis, and so there is good knowledge of safety profiles. A clinical study of HD patients to assess the efficacy and safety of three oral doses of laquinimod has recently been announced (<http://clinicaltrials.gov/show/NCT02215616>). The multicenter, international, placebo-controlled study will last 12 months. Primary outcome measures will include

change UHDRS total motor score and secondary change from baseline in caudate volume, in the HD cognitive assessment battery, in the UHDRS total functional capacity, and in the Clinician's Interview-Based Impression of Change.

## Development of symptomatic therapies

Even given the exciting developments of therapies aimed at changing the course of the disease, the search for symptomatic drugs specifically targeted for HD remains important. In this context, the increased knowledge of the disturbed signaling mechanisms in the HD brain allows a further development from a nonspecific approach based on a generalization from studies in disorders with similar symptoms but different etiologies toward more specific ones. Until recently, few high-quality clinical trials had been performed specifically for the treatment of symptoms in HD patients,<sup>69</sup> and a wide range of drugs used, due to a lack of consensus.<sup>70</sup> Tetrabenazine was the first drug to be approved for symptomatic treatment in HD, in this case chorea. The drug inhibits the vesicular monoamine transporter (VMAT), and at doses up to 100 mg per day UHDRS chorea,<sup>71</sup> and improves global clinical impression, with a clear deterioration after withdrawal.<sup>72</sup> Tetrabenazine, a compound with <sup>2</sup>H substitution of hydrogen to decrease metabolisms, is now being studied to assess safety, tolerability, and efficacy for treating chorea (<http://clinicaltrials.gov/show/NCT01795859>), and in an open label long-term study to examine long-term safety (<http://clinicaltrials.gov/show/NCT01897896>). In a single double-blind study specifically devoted to the treatment of cognitive impairment in HD, latrepirdine for 6 months did not improve cognition or function.<sup>73</sup>

Pridopidine has a state-dependent effect on D<sub>2</sub> dopamine receptors, with rapid dissociation kinetics providing interesting properties to regulate striatal function in HD. The drug has been studied in two studies,<sup>74,75</sup> which failed to reach primary end points, but did so for a secondary outcome: the total UHDRS motor score. A new study examining a larger range of doses has been launched in a multicenter, multinational, randomized, parallel-group, double-blind, placebo-controlled design to compare safety and efficacy in the treatment of motor impairment (<http://clinicaltrials.gov/show/NCT02006472>).

Muscle pathology is well documented in HD, with gradual generalized atrophy due to a number of mechanisms, including primary myopathology.<sup>76,77</sup> Inhibition of a regulatory pathway linked to myostatin leads to muscle hypertrophy, and this can be performed by several modalities, including receptor decoy

and specific antibodies against the myostatin ligand, substances in clinical development for a number of indications. Indeed, in an HD mouse, a profound recovery of muscle loss was induced with an ActRIIB-receptor decoy, and this led to a functional improvement with increased grip strength.<sup>78</sup>

## Conclusion

The field of translational research in HD is a fast-moving area, and has now led to a number of avenues with reasonably valid promise to develop therapies aimed at postponing the start and the course of the disorder. However, given the complex pathophysiology of the disorder, it is very likely that a future therapy will combine a number of drugs targeting different molecular targets in order to both improve symptoms and afford neuroprotection. Such complex therapies are well known in other disorders, such as human immunodeficiency virus, diabetes, and hypertension. Since the single cause of HD is precisely known, and can be confirmed long before onset, this disorder may be considered a paradigm for disease-modifying treatment of other neurodegenerative disorders. This has fostered the interest of researchers, pharmaceutical companies, and sponsors alike.

## Disclosure

The author reports no conflicts of interest in this work.

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