Published in final edited form as:
Neurotherapeutics. 2008 April ; 5(2): 226–236.

Neuroprotection For Huntington's Disease: Ready, Set, Slow

Steven M. Hersch[*] and **H. Diana Rosas**[†]

[*]*MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129-4404*

[†]*Center for Neuroimaging of Aging and Neurodenerative Diseases, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129-4404*

Summary

The ultimate goal for Huntington's disease (HD) is to develop disease-modifying neuroprotective therapies able to delay or prevent illness in those who are at genetic risk and able to slow progression in those who are affected clinically. Neuroprotection is the preservation of neuronal structure, function, and viability and neuroprotective therapy is thus targeted at the underlying pathology of HD, rather than at its specific symptoms. Preclinical target discovery research in HD is identifying numerous distinct targets and options for modulating them with some proceeding into large-scale efficacy studies in early symptomatic HD subjects. The first pilot studies of neuroprotective compounds in premanifest HD are also soon to begin. This review discusses the opportunities for neuroprotection in HD, clinical methodology in premanifest and manifest HD, the clinical assessment of neuroprotection, molecular targets and therapeutic leads, and the current state of clinical development.

Keywords

Huntington's disease; neuroprotection; disease modification; neurogenetics; genetic testing; clinical trials; presymptomatic; premanifest

Introduction

The ultimate goal for HD is to develop disease-modifying neuroprotective therapies capable of delaying or preventing clinical illness in those who are at genetic risk, and capable of slowing progression and permitting some recovery in those who have clinical illness. Neuroprotection can be defined quite literally as the preservation of neuronal structure, function, and viability, or more generically as the slowing or prevention of neurodegeneration. Neuroprotective therapy is thus targeted at the underlying pathology of HD, rather than at its specific symptoms. The assumption we make is that selecting treatments based on their ability to limit neuropathology will be complementary to, and ultimately more fundamentally beneficial, than selecting treatments based on their ability to suppress symptoms. Basic and translational research in HD is creating an expanding pipeline of candidate neuroprotective therapies that are beginning to be tested in early and late-phase clinical trials. Candidate therapies are

Corresponding author: Steven M. Hersch, MD, PhD, MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital, Harvard Medical School, MGH East, Bldg. 114, Room 2005,114 16th St., Charlestown, MA 02129-4404; Ph: (617) 726-1254, Fax: (617) 724-1480; hersch@helix.mgh.harvard.edu.

generally filtered through genetic mouse models of HD and when supportive preclinical data demonstrates significant neuroprotection, a compound is considered for advancement to clinical trials. The therapies already on this pathway are existing compounds that were selected by a candidate approach connecting hypotheses about mechanisms of disease and existing medications that might modulate them. Commercial and academic efforts that screen compound libraries against elements of the HD phenotype suitable for *in vitro* or cell-based assays are also bringing forward families of novel compounds to be sorted for efficacy, toxicity, and 'drugability'.[1,2] These approaches are expanding the preclinical segment of the pipeline of potential neuroprotective treatments and are beginning to provide new compounds suitable for early-phase clinical testing. This review will provide a framework for the clinical development of neuroprotective therapies for HD and an overview of possible neuroprotective targets and compounds.

Clinical Features and Therapeutic Opportunities

HD is an autosomal, dominant-inherited neurodegenerative disorder that is characterized by progressive motor dysfunction, emotional disturbances, dementia, and weight loss. HD occurs worldwide in all races and ethnic groups.[3] Its prevalence is 5 to 10 cases per 100,000, and there is a new mutation rate as high as 1–3%.[4,5] There are about 30,000 affected individuals in North America while another 150,000 have a genetic risk for developing the disease. The incidence of being gene mutation-positive in the at-risk population is about 40% (60,000 individuals), because of individuals being diagnosed and depleting the pool of potential gene-positive individuals. The average age of clinical onset is about 37 years of age; however, the range is from infancy into the 80s. Affected individuals are disabled by early functional decline and require increasing levels of care and support usually requiring residential long-term care[6] and surviving about 15–25 years from the time of diagnosis before succumbing to the effects of severe physical and mental deterioration. Symptomatic therapies are few and have limited impact.[7,8] There is no therapy proven to delay onset or slow progression[9,10] and the best current medical care has a positive impact by focusing multidisciplinary attention on symptom management and caregiver support, and maximizing function and quality of life.[11–14] Because of early functional decline, the chronic and increasingly intensive care it requires, and its profound multigenerational impact on entire families,[15] HD disproportionately consumes medical, social and family resources. The principal target populations for neuroprotective therapies are those who are premanifest (not yet symptomatic but known to possess a *huntingtin* gene with the causative CAG expansion) as well as those who are manifest (overtly symptomatic), but not yet so advanced that there is a vastly diminished quality of life to preserve.

Neurodegeneration

HD is caused by the expression of the aberrant huntingtin protein, which contains an abnormally expanded polyglutamine tract near its *N*-terminus.[16] The presence of the abnormal huntingtin protein in cells sets off a complex and poorly understood series of deleterious and progressive biochemical events leading in neurons to stress, physiological dysfunction, compensatory responses, neurodegeneration, and eventually cell death. Neurodegeneration appears to be quite a prolonged process, as evidenced by signs of chronic neuroplasticity[17,18] and of the slow involution of neurons with gradual loss of synapses, dendritic spines, dendritic branches, axonal segments, and supportive cytoplasmic resources like mitochondria and organelles involved in the biosynthesis, modification, transport, and degradation of cellular molecules. The process of neurodegeneration ends in cell death, and dead and dying neurons *in situ* can cause local inflammatory responses and possibly worsen conditions in their immediate vicinity. Because neurons exist to influence one another, as well as the periphery, the neurodegenerative process can profoundly affect networks of interconnected neurons and

the neurochemical, electrophysiological, and trophic lines of communication and regulation that underlie neuronal and neurological function. The progressive symptoms of HD clearly are caused by the functional network effects of neurodegeneration and neuronal death in many brain regions and the depletion of the brain's reserve to compensate.

Location confers both function and dysfunction in the brain and one neuropathologic hallmark of the neurodegeneration and cell death in HD is regional and cellular selectivity.[19] The earliest and most aggressive neuropathologic changes are found in the neostriatum. As a result, there is a long tradition of ascribing the broad range of neurologic symptoms that occur in HD to basal ganglia circuitry and excessive conviction that protecting the striatum is the principal goal of neuroprotective therapy. Striatal neurodegeneration undoubtedly provides a significant component of the early HD phenotype; marked neuronal loss has, however, been identified in many other regions of the brain[19] and phenotypes associated with damage to them are significant in HD. For example, the involvement and clinical contributions of cerebral cortical neurodegeneration have recently become more fully appreciated. Neuroimaging techniques are showing that cortical neurodegeneration is early, heterogeneous, progressive, and correlates strongly with HD symptoms.[20,21] It seems likely that cortical dysfunction and degeneration play significant roles in the motor control, cognitive, and psychiatric symptoms of HD and in the heterogeneous evolution of clinical symptoms as neurodegeneration plays out involving more and more of the cerebral cortex. An important implication is that cell replacement, trophic support, RNA interference, or other potential neuroprotective treatments that might be focally applied to the striatum may have very have limited usefulness.

Neuroprotection in Premanifest HD

Individuals destined to develop HD are born with the HD genetic mutation. Because the abnormal huntingtin protein is present, it is possible that there are biochemical or other abnormalities present from birth. However, all existing information suggests that most of these individuals experience a period of apparent clinical and biological normalcy before entering a prodromal period in which there is active underlying disease without any evident clinical or functional consequences. Current evidence indicates that the causative processes involved in HD are present for at least 10 to 20 years before HD can be diagnosed clinically[21–28] on the basis of the unequivocal presence of the movement disorder. The transition from HD prodrome to manifest HD (an expression of diagnostic certainty by the assessing physician) is termed 'phenoconversion'.[29] Progressive atrophy of the striatum and cerebral cortex has been well documented to occur in the premanifest prodrome period indicating that the neurodegenerative process is occurring during premanifest HD.[21,28,30] Subtle cognitive, motor, psychiatric,[31–33] and metabolic abnormalities[34,35] are detectable in premanifest HD and biochemical alterations are beginning to be detected in blood.[24,36] It is unknown whether the HD prodrome represents a stable condition until some decompensation causes manifest HD to emerge or whether it is a continuum in which clinically silent neurodegeneration gradually accumulates sufficiently to cause unequivocal symptoms. The pace of the disease process could certainly vary at different times or be accelerated by other stresses. For example, we have observed clinical onset to be hastened by significant traumatic brain injury. Regardless, it seems desirable to begin a neuroprotective therapy before or during the prodrome with the aim of delaying onset, as well as slowing progression of the underlying pathologic processes while they are still subclinical. This should not be considered 'prevention' since the treatment is aimed at active disease. Since there are about five times as many at-risk as symptomatic individuals, an even larger ratio of potential years of treatment and probably less to gain from treating the most advanced individuals, the premanifest population represents the largest therapeutic opportunity for HD for neuroprotection. In addition, since symptomatic individuals are generally unable to work within a few years, delaying their disability and dependence would have great economic and social benefits.

Two large ongoing observational trials (PHAROS, PREDICT-HD)[29,37] conducted by the Huntington Study Group (HSG) were conceived to help design and power efficacy trials in this population and will be completed soon. These studies will help determine how to power a neuroprotection study seeking to delay onset based on an expected rate or time of phenoconversion.[38,39] In addition, there is active research examining possible biomarkers that could provide endpoints for detecting and monitoring progression during the HD prodrome. The first pilot interventional studies in presymptomatic individuals using putative neuroprotective compounds will be underway this year. Because premanifest individuals are healthy and fully functional, the period of neuroprotective treatment for these individuals could be for decades. Therefore, the ideal intervention would require a very high level of safety and tolerability. Accordingly, CoQ_{10} and creatine, which are capable of ameliorating energy depletion and whose efficacy in manifest HD will be known in a few years, have been suggested by SET-HD (an independent program to identify, systematically assesses, and prioritize experimental therapies for HD; http://www.huntingtonproject.org) to be appropriate for examination in premanifest HD and they will be tested first in separate NIH-supported studies examining safety, tolerability, dosing, and biomarkers.

An important issue in designing a neuroprotection trial in the premanifest population is the fact that the vast majority of these individuals (>95%) have not desired genetic testing.[40] Some reasons for this include fear of genetic discrimination,[41] the lack of effective treatment, and concern about the negative consequences of genetic testing.[42,43] Focus groups with at-risk individuals have revealed that many would be adverse to taking part in clinical trials if informative genetic testing is required. Similarly, many would willingly take an experimental medication and risk side effects in a clinical trial *without* genetic testing, understanding that there would be about a 60% chance of not having the gene mutation. Performing a clinical trial only in subjects who have had genetic testing is feasible for smaller scale, early-phase studies. However, without a dramatic upsurge in genetic testing, it is difficult to imagine that sufficient subjects are available for most efficacy designs seeking evidence for neuroprotection. The population of available premanifest subjects who have had testing may also not be fully representative of the at-risk population. Requiring genetic testing for entry into a desirable clinical trial raises an important ethical concern about creating a coercive incentive for genetic testing along with its negative consequences in subjects wishing to participate. To allay this concern and also to have normal controls for tolerability and biomarker measures, an option is to allow the enrollment of individuals who are either at-risk for HD by virtue of having a first degree relative with HD or who have tested positive for the HD gene mutation. Approximately 60% of the former would be gene negative, while all of the latter would be gene positive. This novel design would greatly neutralize any incentive for genetic testing. If a high level of safety and tolerability can be expected from the intervention, treating gene negative individuals is preferable to coercing genetic testing which carries its own risks.[44] A design to perform double-blinded genetic testing and provide placebo to gene negative individuals and active compound to gene positive individuals might also be feasible, although complicated to administer. These will be important considerations in designing clinical trials in premanifest HD for which there is no road map.

Neuroprotection in Manifest HD

Once diagnosed clinically, individuals with HD have a highly variable phenotype. Different affected individuals can have predominant motor (chorea, dystonia, bradykinesia), predominant cognitive (executive dysfunction) or predominant psychiatric (depression, emotional dyscontrol, psychosis, obsessive-compulsive symptoms) presentations. Symptom severity can be modulated by many temporary factors such as mood, nutrition, medications, and sleep disturbances. Accordingly, treatments benefiting symptoms may or may not do so on the basis of neuroprotection. Additionally, each symptom in HD has its own temporal

course, including onset, progression, plateau, and waning – most likely because the neurodegeneration occurring in the brain regions that underlie the symptoms reaches some point where its clinical expression has little room to progress further. For example, chorea may be present early, worsen for some years, stabilize, and wane as it is supplanted by dystonia and spasticity. Regional cerebral cortical neurodegeneration in HD is heterogenous in time and location and may explain some of the differences between patients as well as the evolution of symptoms in time, despite the early and stereotypical decimation of the striatum.[20]

Despite the great day-to-day variability in symptoms and their uneven evolution over time, the overall clinical progression of HD is slow when assessed by an integrated measure of functional capacity (e.g., the Total Functional Capacity scale, TFC[45]). Clinical trials in early symptomatic HD include subjects with a TFC of about 7 or greater. This encompasses a phenotypic range of normal; to impaired but functional at home and work; to unable to work but independent at home; to needing some assistance at home but still ambulatory, independent for ADLs, and competent to direct their activities. These subjects retain a high quality of life and slowing their decline would delay loss of independence and the need for an escalation in care resources, including residential long-term care. From the time an individual is diagnosed as having unequivocal clinical symptoms, it takes about 5–10 years for the TFC to decline to 7 from a normal score of 13. There is sufficient phenotypic range in this population to observe progression and its slowing by a disease-modifying treatment, and power calculations are currently based on this information.

Measurement of Neuroprotection and Treatment Approval

Neuroprotection can be defined as a beneficial treatment effect on a biological process that contributes to neurodegeneration in HD and thus to clinical progression. There are many possibilities for measuring such effects which must be considered carefully when designing a clinical trial. In early-phase clinical trials, evidence for potential efficacy may be of secondary interest if examining dosing, pharmacokinetics, pharmacodynamics, safety, and tolerability are the principal objectives. Preliminary evidence of potential neuroprotective efficacy from early-phase studies, however, can be vital for decisionmaking about whether to continue the development of the treatment into large and expensive Phase III studies. A great need for HD has been clinical or other outcome measures able to provide that preliminary evidence. Indeed, without such signals it is also very difficult to stop development of a compound short of its failure in a large-scale study. Clinical measures, such as those contained in the UHDRS can show an effect on HD symptoms, though symptomatic (either better or worse) and neuroprotective effects cannot be considered to be synonymous. Global clinical measures that correspond to disease progression, such as the TFC or other indicators of functional decline, are insensitive measures in typical early-phase studies involving anywhere from a few to 100 subjects, and durations measured in weeks to months. There are refined, often quantitative, clinical measures of motor and cognitive dysfunction that can be sensitively measured in HD subjects, including premanifest subjects. Some of these could be surrogates for measuring progression of the underlying disease and serve as indicators of the disease-modifying potential of a treatment. Since it is difficult to relate response magnitudes for such measures to clinically significant benefits, they are not yet useable as primary endpoints for assessing efficacy. Even more promising are biomarkers from neuroimaging or from biological samples or fluids (‘wet’ biomarkers) that could provide measures of disease activity or progression. To the extent these suggest a neuroprotective effect, they can be quite supportive of decisions about whether a compound should continue in development. Biomarkers are especially promising for this, as neuroimaging showing slowed regional or whole brain atrophy or ‘wet’ biomarkers showing a pharmacodynamic response are especially close to the biology of neurodegeneration, can be revealing in premanifest or manifest HD, and may have sufficient sensitivity in small sample size studies. It must also be kept in mind that brain volumes could be affected by a treatment

without an accompanying effect on neurodegeneration and that 'wet' biomarkers may capture only limited aspects of the entire biochemistry underlying neurodegeneration and thus may not be predictive of a significant clinical response later. Regardless, such indicators of potential benefits that could best be explained by disease modification should increase the likelihood of demonstrating efficacy in a Phase III study. At the same time, negative findings can help in decisionmaking about whether the likelihood of a neuroprotective effect seems too low to invest further in a potential treatment. In the absence of accepted biomarkers, an alternative for seeking preliminary evidence of efficacy is the 'futility' design[46] in which the TFC can still be used as the primary outcome measure, but the prespecified indicator is sufficient divergence between it and a standard derived from historical or limited placebo controls such that the probability of the two groups being different crosses a threshold indicating that some minimal difference is likely. An ongoing futility study examining minocycline in HD will enroll 124 subjects, who will be followed for 18 months. Such studies are still relatively large and 'non-futility' won't normally count as a demonstration of efficacy for regulatory purposes, despite the investment.

The FDA considers treatments for approval that are sufficiently demonstrated as providing a significant clinical benefit. Slowing of the TFC has been acceptable to the FDA as the primary outcome measure in efficacy studies designed to determine if a treatment slows functional decline, an integrated clinical reflection of neuroprotection. Currently, efficacy studies in symptomatic patients with HD using the TFC as the primary outcome requires about 650 subjects and 3 years of follow-up to detect a 25% slowing of decline (1:1 randomized placebo controlled trial, and assuming 10–15% dropouts). Other global clinical measures such as quality of life scales or functional disability measures could likewise serve as outcome measures reflecting disease modification or neuroprotection during manifest HD, and measures with greater power than the TFC would enable testing more treatments. The expense, time, and great magnitude of effort needed to test efficacy means that few interventions can be tested. Furthermore, having large numbers of subjects on placebo treatment for years in these trials is an unfortunate necessity. Biomarkers of disease biological activity can be used to help answer whether treatments have the desired pharmacologic effects and whether there are potential explanations for response heterogeneity. Biomarkers corresponding to disease progression that could help assess efficacy could supplement the TFC or other clinical measures as secondary endpoints and, if qualified, may ultimately serve as surrogate endpoints for regulatory purposes enabling the testing of disease modification in fewer subjects more quickly. These would have to first be qualified in successful neuroprotection trials, but they could enable more efficient testing of more potential neuroprotective therapies in the future. It is a high priority to take every available opportunity to study possible biomarkers in therapeutic trials to bring that day closer.

No measures of clinical impact suitable for regulatory approval exist for premanifest HD since these individuals have no disability to measure, even if they have measurable symptoms or signs.[47] Presently, an efficacy study in premanifest HD would have to be designed to slow the rate of phenoconversion to meet a regulatory standard of demonstrating a clinical benefit. To examine whether a treatment delays the onset of clinical symptoms in premanifest individuals with the HD genetic mutation, it has been estimated that a daunting 1000–3000 subjects and 3–6 years of follow-up would be necessary to detect even a large 30–40% decline in the frequency of symptom onset. A regulatory approval for a neuroprotective treatment based on studies in manifest HD could be applicable to premanifest HD, since there is no reason to think premanifest and manifest HD differ biologically. However, regulators could view concerns about safety differently in premanifest and manifest individuals such that toxicity acceptable in symptomatic individuals might not be considered acceptable in asymptomatic individuals. There might also be additional concerns about treating healthy individuals for many years before symptoms occur because of uncertainty about long-term toxicity and also uncertainty

about identifying the period in which it is necessary to treat for the clinical benefit of delayed onset. Thus, a treatment could potentially be approved with an indication for symptomatic individuals specifically though — once approved — a treatment will be in the hands of prescribers.

Biomarkers could provide pharmacodynamic indicators of disease slowing in premanifest HD in the absence of clinical symptoms and provide evidence of disease modification in smaller-scale trials. Ideally, biomarkers indicating subclinical disease activity or clinical predictors of future disease onset could eventually help decisionmaking in practice about when to start a neuroprotective treatment in premanifest HD. A potential strategy to include premanifest individuals in clinical research and in the approval process is to perform pivotal Phase III efficacy studies in early manifest HD and supplement these with limited studies examining safety, tolerability, and biomarkers of disease progression in premanifest HD. Should a treatment prove efficacious in manifest HD and similarly affect biomarkers of disease progression in premanifest and manifest HD, it may be possible to build a rationale for not excluding premanifest individuals in the treatment label. There is as yet no clear road map for regulatory approaches for an indication to treat premanifest HD.

The Role of Preclinical Genetic Mouse Models in Initiating Neuroprotection Trials

Candidate neuroprotective treatments for HD can be tested in proof-of-concept studies using genetic mouse models of HD (transgenic mice expressing part or all of an exogenous mutant huntingtin or knockin mice in which the polyglutamine tract in the HD gene is pathologically expanded). Positive results in these models have promoted go-ahead decisions in industry and academia for clinical trials in HD subjects. The predictive value of the mouse models, though logical, has not yet been validated because there have not yet been sufficient efficacy studies in humans testing compounds effective in them to do so. There is also a history of disappointment with predictability from animal models of other neurologic diseases, such as stroke and ALS. We think HD models may be more representative of the disease given their underlying genetic fidelity. There are other reasons, in addition to model accuracy, that mouse data may not scale to human such as inherent biological differences and bioequivalence differences with the treatment. Currently, it is fair to state that positive mouse data may not predict efficacy and negative mouse data may not predict failure. Nevertheless, positive data in mouse models can be supportive when considering all of the factors around the potential rationale for testing a putative neuroprotective treatment in human HD. There are several categories of data that can be obtained in preclinical models that can be helpful. The least helpful is positive or negative behavioral or motor performance data because the outcome measures can be influenced pharmacologically without impacting neuroprotection (preservation of neuronal structure, function, and viability). Since neurodegeneration is defined neuropathologically, neuropathologic indicators of neuroprotection provide the most useful proof-of-concept information. These include measures such as brain weight, atrophy, ventricular size, neuronal size, and neuronal number, and there are established means for measuring each of these. Modulation of the presence of huntingtin protein aggregates in brain does not correlate strictly to toxicity or to neuroprotection but can provide information about how the treatment affects huntingtin itself. Behavioral data has much more meaning in the context of the underlying neuropathology, which enables interpreting it in relation to neuroprotection. Other types of studies in HD mice can help fill in understanding about how neuroprotection might occur (or fail) and by modeling potential biomarkers. Despite the uncertain predictive value of positive data in HD mouse models, there are some principles for assessing its usefulness, especially in the setting of an HD research community with a lot of focus on such studies. At the simplest level, any positive evidence for neuroprotection (neuropathology) is better than none. Most negative data is not as compelling as positive data

because there are many more alternative explanations for achieving the former than the latter. Negative studies in HD mouse models are quite easily achieved and rarely published, and there are many reasons these may not reflect the neuroprotective potential of a compound. These can include the fidelity of the model, genotype or strain effects, experimental conditions, the many variables that relate to optimal brain bioavailability, and methodological errors. For positive results, the more rigor the better in terms of methodology, limitation of bias, replication, controls, and exposure to peer review. Replication is especially powerful for confirming a result and this could be in different cohorts, in different labs, in alternative mouse models, or by using distinct but related compounds. Ideally, positive evidence for neuroprotection from more than one laboratory, more than one mouse model, using neuropathology outcome measures, and using more than one compound provide the maximal preclinical proof-of-concept support. Lesser levels of evidence than this ideal can certainly be supportive and their limitations understood when formulating how the mouse data contributes to decisionmaking about translation to human testing, where many other considerations come into play.

Candidate Targets for Neuroprotection

HD is caused by the expression of the abnormal huntingtin protein which contains an expanded polyglutamine tract near its *N*-terminal. Although many leads have been uncovered, a stepwise pathway from huntingtin to neuronal dysfunction and death has not been established. Huntingtin is a widely expressed, predominantly cytoplasmic, protein of unknown function found heterogeneously in neurons throughout the brain and widely in the body.[48–52] In HD, both normal and mutant alleles are expressed and both gain of function alterations in which mutant huntingtin is toxic and loss of function alterations[53–55] in which suppression of normal huntingtin functions might also be toxic have been identified. Proteolysis of mutant huntingtin, whereby abnormal and ultimately toxic *N*-terminus fragments of huntingtin are released,[56–59] seems to play a dominant role in causing disease.[60] Most evidence points to a proximal toxicity residing in mutant huntingtin or its proteolytic fragments and their soluble interactions with other proteins, including huntingtin itself or the hundreds of other proteins that have been demonstrated to associate with huntingtin.[61] Proximal events mediated by mutant huntingtin in turn trigger cascades of both damaging and compensatory molecular processes and genetic programs. These events and sequelae include mitochondrial dysfunction, energy depletion,[62–64] oxidative stress,[65,66] DNA damage,[67] synaptic stress,[68] disordered neurophysiology,[69] proapoptotic signals,[70] protein aggregation,[71–73] malfunctioning proteolysis,[74] autophagy,[75–79] ubiquitin/proteosomal function[MD1],[80–82] neurotrophin deficiency,[83–85] and disrupted intracellular transport[86] — all of which might play a role in neuronal death.[87] The presence of huntingtin or its fragments in the nucleus seems to particularly drive pathology.[88,89] This is likely due to interactions in the nucleus with a variety of transcription factors and regulators leading to complex and multifaceted transcriptional alterations that also seem important to pathogenesis and reverberate through cellular biochemistry.[90–101] These complex processes ultimately lead to increasingly fragile, atrophic, dysfunctional neurons that ultimately die. These processes have suggested many potential therapeutic targets (Table 1), some of which have had some preclinical validation through studies in HD transgenic mice and which are represented in the increasing pipeline of possible disease-modifying therapies. What is uncertain is the relative importance and interdependence of each, though reducing levels of mutant huntingtin — for example, by RNA interference[102–106], suppressing its cleavage,[60] improving its misfolding,[107] or reducing its nuclear transport — might be the most fundamental (proximal).

Candidate Therapies for Huntington's Disease

Not all of the potential neuroprotective targets in Table 1 have been subjected to proof-of-concept studies in HD mouse models. However, preclinical studies in HD transgenic mice have provided a basis for testing a growing list of compounds in HD. Included are compounds that enhance mitochondrial function or suppress oxidative injury, such as coenzyme Q10,[108] creatine,[109,110] dicholoracetate,[111] alpha-lipoic acid,[112] the antiapoptotic antibiotic minocycline,[113] the transglutaminase inhibitor cystamine,[114, 115] metal chelators;[116, 117] glutamate antagonists and other neurotransmitter modulators such as Remacemide, Riluzole,[118,119] and paroxetine[120]; transcriptionally active compounds such as histone deacetylase inhibitors, and DNA intercalating agents,[121–124] and agents (e.g., RNA interference) for blocking the translation of huntingtin protein itself;[102–106] and Tauroursodeoxycholic acid (TUDCA)[125] or other agents that might act by increasing BDNF levels, which has been implicated repeatedly in HD[126] but its potential as a therapeutic target remains untested. There are so many potential disease-modifying therapies that they are not reviewed exhaustively here. The reader is instead referred to the SET-HD website (http://www.huntingtonproject.org), an independent effort to identify, systematically assess, and prioritize experimental therapies for HD.

Most clinical trials to date in humans with HD have focused on preventing oxidative and glutamatergic stress. These studies, many of which were multi-center trials organized by the Huntington Study Group (HSG), included the anti-oxidants idebenone, vitamin E,[127–129] creatine,[130,131] coenzyme Q_{10} (CoQ_{10}),[132] the antioxidant transglutaminase inhibitor cysteamine,[133] ethyl-EPA,[134] and the glutamate antagonists lamotrigine,[135] remacemide,[132] and riluzole.[119,136,137] These studies have not demonstrated slowing of functional decline, but most have been Phase II studies that were not powered to test efficacy. In the CARE-HD (CoQ_{10} and Remacemide Evaluation in Huntington's Disease) study completed by the HSG, a trend toward slowed progression was observed with CoQ_{10} while remacemide, though not affecting progression, appeared to improve chorea.[132] Interestingly, the rates of slowed progression in CARE-HD and survival prolongation in the mice treated with CoQ_{10} were the same, about 14%. Remacemide was neuroprotective in mice but not in CARE-HD, but the maximally tolerated doses used were much greater in mice than in humans. Thus, there is some evidence that preclinical results in mice may be predictive of therapeutic responses in humans. Given the encouraging preliminary results in CARE-HD, a series of studies testing the pharmacokinetics, safety, and efficacy of higher doses of CoQ_{10} is ongoing. Additional active or planned therapeutic clinical trials for HD in manifest individuals using potential neuroprotective treatments include a high-dose Phase III creatine trial expected to start in 2008, a Phase II trial of phenylbutyrate, the results of which will be reported in 2008, and a futility study using the anti-apoptotic antibiotic minocycline. The incorporation of biomarkers and exploratory clinical outcome measures in these studies should facilitate and improve future neuroprotection trials.

Acknowledgments

The authors are supported by NIH grants from NINDS (P01NS045242, P01NS058793, R01NS04286, U01NS045806, R01HG002449) and NCCAM (R01AT000613, U01AT000613), by the FDA (R01FD003359), HiQ (to HDR), and the HDSA Coalition for the Cure (to SMH).

References

1. Zhang X, Smith DL, Meriin AB, et al. A potent small molecule inhibits polyglutamine aggregation in Huntington's disease neurons and suppresses neurodegeneration in vivo. Proc Natl Acad Sci USA 2005;102:892–897. [PubMed: 15642944]

2. Chopra V, Fox JH, Lieberman G, et al. A small-molecule therapeutic lead for Huntington's disease: preclinical pharmacology and efficacy of C2-8 in the R6/2 transgenic mouse. Proc Natl Acad Sci U S A 2007;104:16685–16689. [PubMed: 17925440]

3. Kremer B, Goldberg P, Andrew SE, et al. A worldwide study of the Huntington's disease mutation. The sensitivity and specificity of measuring CAG repeats. N Engl J Med 1994;330:1401–1406. [PubMed: 8159192]

4. Myers RH, MacDonald ME, Koroshetz WJ, et al. De novo expansion of a (CAG)n repeat in sporadic Huntington's disease. Nat Genet 1993;5:168–173. [PubMed: 8252042]

5. Goldberg YP, Kremer B, Andrew SE, et al. Molecular analysis of new mutations for Huntington's disease: intermediate alleles and sex of origin effects. Nat Genet 1993;5:174–179. [PubMed: 8252043]

6. Dubinsky RM. No going home for hospitalized Huntington's disease patients. Mov Disord 2005;20:1316–1322. [PubMed: 16001414]

7. Bonelli RM, Wenning GK. Pharmacological management of Huntington's disease: an evidence-based review. Curr Pharm Des 2006;12:2701–2720. [PubMed: 16842168]

8. Bonelli RM, Hofmann P. A systematic review of the treatment studies in Huntington's disease since 1990. Expert Opin Pharmacother 2007;8:141–153. [PubMed: 17257085]

9. Hersch SM, Ferrante RJ. Translating therapies for Huntington's disease from genetic animal models to clinical trials. NeuroRx 2004;1:298–306. [PubMed: 15717031]

10. Beal MF, Ferrante RJ. Experimental therapeutics in transgenic mouse models of Huntington's disease. Nat Rev Neurosci 2004;5:373–384. [PubMed: 15100720]

11. Hersch, S.; Greenamyre, J. Huntington's Disease. In: Johnson, R.; Griffin, J., editors. Current Therapy in Neurologic Disease. St. Louis: Mosby-Year Book Inc; 1996. p. 51-55.

12. Anderson KE, Marder KS. An overview of psychiatric symptoms in Huntington's disease. Curr Psychiatry Rep 2001;3:379–388. [PubMed: 11559474]

13. Rosenblatt, A.; Ranen, N.; Nance, M.; Paulsen, J. A physician's guide to the management of Huntington's Disease. 2 ed.. New York: Huntington's Disease Society of America; 1999.

14. Simpson SA. Late stage care in Huntington's disease. Brain Res Bull 2007;72:179–181. [PubMed: 17352944]

15. Vamos M, Hambridge J, Edwards M, Conaghan J. The impact of Huntington's disease on family life. Psychosomatics 2007;48:400–404. [PubMed: 17878498]

16. 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;72:971–983. [PubMed: 8458085]

17. Ferrante RJ, Kowall NW, Richardson EP Jr. Proliferative and degenerative changes in striatal spiny neurons in Huntington's disease: a combined study using the section-Golgi method and calbindin D28k immunocytochemistry. J Neurosci 1991;11:3877–3887. [PubMed: 1836019]

18. Sotrel A, Williams RS, Kaufmann WE, Myers RH. Evidence for neuronal degeneration and dendritic plasticity in cortical pyramidal neurons of Huntington's disease: a quantitative Golgi study. Neurology 1993;43:2088–2096. [PubMed: 8413971]

19. Hersch, S.; Ferrante, R. Neuropathology and Pathophysiology of Huntington's Disease. In: Watts, R.; Koller, W., editors. Movement Disorders. Neurologic Principles and Practice. New York: McGraw-Hill; 1997. p. 503-526.

20. Rosas HD, Liu AK, Hersch S, et al. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology 2002;58:695–701. [PubMed: 11889230]

21. Rosas HD, Hevelone ND, Zaleta AK, Greve DN, Salat DH, Fischl B. Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. Neurology 2005;65:745–747. [PubMed: 16157910]

22. Aylward EH, Codori AM, Barta PE, Pearlson GD, Harris GJ, Brandt J. Basal ganglia volume and proximity to onset in presymptomatic Huntington disease. Arch Neurol 1996;53:1293–1296. [PubMed: 8970459]

23. Aylward EH, Codori AM, Rosenblatt A, et al. Rate of caudate atrophy in presymptomatic and symptomatic stages of Huntington's disease. Mov Disord 2000;15:552–560. [PubMed: 10830423]

24. Borovecki F, Lovrecic L, Zhou J, et al. Genome-wide expression profiling of human blood reveals biomarkers for Huntington's disease. Proc Natl Acad Sci U S A 2005;102:11023–11028. [PubMed: 16043692]
25. Gomez-Tortosa E, MacDonald ME, Friend JC, et al. Quantitative neuropathological changes in presymptomatic Huntington's disease. Ann Neurol 2001;49:29–34. [PubMed: 11198293]
26. Paulsen JS, Zimbelman JL, Hinton SC, et al. fMRI biomarker of early neuronal dysfunction in presymptomatic Huntington's Disease. AJNR Am J Neuroradiol 2004;25:1715–1721. [PubMed: 15569736]
27. Reading SA, Dziorny AC, Peroutka LA, et al. Functional brain changes in presymptomatic Huntington's disease. Ann Neurol 2004;55:879–883. [PubMed: 15174024]
28. Rosas HD, Tuch DS, Hevelone ND, et al. Diffusion tensor imaging in presymptomatic and early Huntington's disease: Selective white matter pathology and its relationship to clinical measures. Mov Disord 2006;21:1371–1325.
29. At risk for Huntington disease: The PHAROS (Prospective Huntington At Risk Observational Study) cohort enrolled. Arch Neurol 2006;63:991–996. [PubMed: 16831969]
30. Aylward EH. Change in MRI striatal volumes as a biomarker in preclinical Huntington's disease. Brain Res Bull 2007;72:152–158. [PubMed: 17352939]
31. Julien CL, Thompson JC, Wild S, et al. Psychiatric disorders in preclinical Huntington's disease. J Neurol Neurosurg Psychiatry 2007;78:939–943. [PubMed: 17178819]
32. Marshall J, White K, Weaver M, et al. Specific psychiatric manifestations among preclinical Huntington disease mutation carriers. Arch Neurol 2007;64:116–121. [PubMed: 17210818]
33. Duff K, Paulsen JS, Beglinger LJ, Langbehn DR, Stout JC. Psychiatric Symptoms in Huntington's Disease before Diagnosis: The Predict-HD Study. Biol Psychiatry 2007;62:1341–1346. [PubMed: 17481592]
34. Klepac N, Relja M, Klepac R, Hecimovic S, Babic T, Trkulja V. Oxidative stress parameters in plasma of Huntington's disease patients, asymptomatic Huntington's disease gene carriers and healthy subjects : A cross-sectional study. J Neurol. 2007
35. Saft C, Zange J, Andrich J, et al. Mitochondrial impairment in patients and asymptomatic mutation carriers of Huntington's disease. Mov Disord 2005;20:674–679. [PubMed: 15704211]
36. Varani K, Abbracchio MP, Cannella M, et al. Aberrant A2A receptor function in peripheral blood cells in Huntington's disease. Faseb J 2003;17:2148–2150. [PubMed: 12958155]
37. Paulsen JS, Hayden M, Stout JC, et al. Preparing for preventive clinical trials: the Predict-HD study. Arch Neurol 2006;63:883–890. [PubMed: 16769871]
38. Langbehn DR, Brinkman RR, Falush D, Paulsen JS, Hayden MR. A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. Clin Genet 2004;65:267–277. [PubMed: 15025718]
39. Langbehn DR, Paulsen JS. Predictors of diagnosis in Huntington disease. Neurology 2007;68:1710–1717. [PubMed: 17502553]
40. Tibben A, Niermeijer MF, Roos RA, et al. Understanding the low uptake of presymptomatic DNA testing for Huntington's disease. Lancet 1992;340:1416. [PubMed: 1360126]
41. Penziner E, Williams JK, Erwin C, et al. Perceptions of discrimination among persons who have undergone predictive testing for Huntington's disease. Am J Med Genet B Neuropsychiatr Genet. 2007
42. Lilani A. Ethical issues and policy analysis for genetic testing: Huntington's disease as a paradigm for diseases with a late onset. Hum Reprod Genet Ethics 2005;11:28–34. [PubMed: 16270448]
43. Robins Wahlin TB. To know or not to know: a review of behaviour and suicidal ideation in preclinical Huntington's disease. Patient Educ Couns 2007;65:279–287. [PubMed: 17000074]
44. Timman R, Roos R, Maat-Kievit A, Tibben A. Adverse effects of predictive testing for Huntington disease underestimated: long-term effects 7–10 years after the test. Health Psychol 2004;23:189–197. [PubMed: 15008664]
45. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. Huntington Study Group. Neurology 2000;54:452–458. [PubMed: 10668713]

46. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology 2006;66:664–671. [PubMed: 16481597]
47. Witjes-Ane MN, Mertens B, van Vugt JP, Bachoud-Levi AC, van Ommen GJ, Roos RA. Longitudinal evaluation of "presymptomatic" carriers of Huntington's disease. J Neuropsychiatry Clin Neurosci 2007;19:310–317. [PubMed: 17827417]
48. DiFiglia M, Sapp E, Chase K, et al. Huntingtin is a cytoplasmic protein associated with vesicles in human and rat brain neurons. Neuron 1995;14:1075–1081. [PubMed: 7748555]
49. Gutekunst CA, Li SH, Yi H, Ferrante RJ, Li XJ, Hersch SM. The cellular and subcellular localization of huntingtin-associated protein 1 (HAP1): comparison with huntingtin in rat and human. J Neurosci 1998;18:7674–7686. [PubMed: 9742138]
50. Persichetti F, Ambrose CM, Ge P, et al. Normal and expanded Huntington's disease gene alleles produce distinguishable proteins due to translation across the CAG repeat. Mol Med 1995;1:374–383. [PubMed: 8521295]
51. Sharp AH, Loev SJ, Schilling G, et al. Widespread expression of Huntington's disease gene (IT15) protein product. Neuron 1995;14:1065–1074. [PubMed: 7748554]
52. Trottier Y, Devys D, Imbert G, et al. Cellular localization of the Huntington's disease protein and discrimination of the normal and mutated form. Nat Genet 1995;10:104–110. [PubMed: 7647777]
53. Cattaneo E, Rigamonti D, Goffredo D, Zuccato C, Squitieri F, Sipione S. Loss of normal huntingtin function: new developments in Huntington's disease research. Trends Neurosci 2001;24:182–188. [PubMed: 11182459]
54. Cattaneo E, Zuccato C, Tartari M. Normal huntingtin function: an alternative approach to Huntington's disease. Nat Rev Neurosci 2005;6:919–930. [PubMed: 16288298]
55. Zuccato C, Ciammola A, Rigamonti D, et al. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 2001;293:493–498. [PubMed: 11408619]
56. Goldberg YP, Nicholson DW, Rasper DM, et al. Cleavage of huntingtin by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract. Nat Genet 1996;13:442–449. [PubMed: 8696339]
57. Wellington CL, Brinkman RR, O'Kusky JR, Hayden MR. Toward understanding the molecular pathology of Huntington's disease. Brain Pathol 1997;7:979–1002. [PubMed: 9217979]
58. Wellington CL, Ellerby LM, Gutekunst CA, et al. Caspase cleavage of mutant huntingtin precedes neurodegeneration in Huntington's disease. J Neurosci 2002;22:7862–7872. [PubMed: 12223539]
59. Hoffner G, Island ML, Djian P. Purification of neuronal inclusions of patients with Huntington's disease reveals a broad range of N-terminal fragments of expanded huntingtin and insoluble polymers. J Neurochem 2005;95:125–136. [PubMed: 16181417]
60. Graham RK, Deng Y, Slow EJ, et al. Cleavage at the caspase-6 site is required for neuronal dysfunction and degeneration due to mutant huntingtin. Cell 2006;125:1179–1191. [PubMed: 16777606]
61. Kaltenbach LS, Romero E, Becklin RR, et al. Huntingtin interacting proteins are genetic modifiers of neurodegeneration. PLoS Genet 2007;3:e82. [PubMed: 17500595]
62. Smith KM, Matson S, Matson WR, et al. Dose ranging and efficacy study of high-dose coenzyme Q10 formulations in Huntington's disease mice. Biochim Biophys Acta 2006;1762:616–626. [PubMed: 16647250]
63. McGill JK, Beal MF. PGC-1alpha, a new therapeutic target in Huntington's disease? Cell 2006;127:465–468. [PubMed: 17081970]
64. Ryu H, Rosas HD, Hersch SM, Ferrante RJ. The therapeutic role of creatine in Huntington's disease. Pharmacol Ther 2005;108:193–207. [PubMed: 16055197]
65. Browne SE, Beal MF. Oxidative damage in Huntington's disease pathogenesis. Antioxid Redox Signal 2006;8:2061–2073. [PubMed: 17034350]
66. Altmann SM, Muryshev A, Fossale E, et al. Discovery of bioactive small-molecule inhibitor of poly adp-ribose polymerase: implications for energy-deficient cells. Chem Biol 2006;13:765–770. [PubMed: 16873024]
67. Kovtun IV, Liu Y, Bjoras M, Klungland A, Wilson SH, McMurray CT. OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells. Nature 2007;447:447–452. [PubMed: 17450122]

68. Stack EC, Dedeoglu A, Smith KM, et al. Neuroprotective effects of synaptic modulation in Huntington's disease R6/2 mice. J Neurosci 2007;27:12908–12915. [PubMed: 18032664]
69. Cepeda C, Hurst RS, Calvert CR, et al. Transient and progressive electrophysiological alterations in the corticostriatal pathway in a mouse model of Huntington's disease. J Neurosci 2003;23:961–969. [PubMed: 12574425]
70. Pattison LR, Kotter MR, Fraga D, Bonelli RM. Apoptotic cascades as possible targets for inhibiting cell death in Huntington's disease. J Neurol 2006;253:1137–1142. [PubMed: 16998646]
71. Davies SW, Turmaine M, Cozens BA, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell 1997;90:537–548. [PubMed: 9267033]
72. DiFiglia M, Sapp E, Chase KO, et al. Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. Science 1997;277:1990–1993. [PubMed: 9302293]
73. Gutekunst CA, Li SH, Yi H, et al. Nuclear and neuropil aggregates in Huntington's disease: relationship to neuropathology. J Neurosci 1999;19:2522–2534. [PubMed: 10087066]
74. Jana NR, Zemskov EA, Wang G, Nukina N. Altered proteasomal function due to the expression of polyglutamine-expanded truncated N-terminal huntingtin induces apoptosis by caspase activation through mitochondrial cytochrome c release. Hum Mol Genet 2001;10:1049–1059. [PubMed: 11331615]
75. Sarkar S, Perlstein EO, Imarisio S, et al. Small molecules enhance autophagy and reduce toxicity in Huntington's disease models. Nat Chem Biol 2007;3:331–338. [PubMed: 17486044]
76. Ventruti A, Cuervo AM. Autophagy and neurodegeneration. Curr Neurol Neurosci Rep 2007;7:443–451. [PubMed: 17764636]
77. Floto RA, Sarkar S, Perlstein EO, Kampmann B, Schreiber SL, Rubinsztein DC. Small molecule enhancers of rapamycin-induced TOR inhibition promote autophagy, reduce toxicity in Huntington's disease models and enhance killing of mycobacteria by macrophages. Autophagy 2007;3:620–622. [PubMed: 17786022]
78. Yamamoto A, Cremona ML, Rothman JE. Autophagy-mediated clearance of huntingtin aggregates triggered by the insulin-signaling pathway. J Cell Biol 2006;172:719–731. [PubMed: 16505167]
79. Ravikumar B, Rubinsztein DC. Role of autophagy in the clearance of mutant huntingtin: a step towards therapy? Mol Aspects Med 2006;27:520–527. [PubMed: 16973207]
80. Seo H, Sonntag KC, Kim W, Cattaneo E, Isacson O. Proteasome activator enhances survival of huntington's disease neuronal model cells. PLoS ONE 2007;2:e238. [PubMed: 17327906]
81. Bennett EJ, Shaler TA, Woodman B, et al. Global changes to the ubiquitin system in Huntington's disease. Nature 2007;448:704–708. [PubMed: 17687326]
82. Howard RA, Sharma P, Hajjar C, et al. Ubiquitin conjugating enzymes participate in polyglutamine protein aggregation. BMC Cell Biol 2007;8:32. [PubMed: 17663792]
83. Zuccato C, Belyaev N, Conforti P, et al. Widespread disruption of repressor element-1 silencing transcription factor/neuron-restrictive silencer factor occupancy at its target genes in Huntington's disease. J Neurosci 2007;27:6972–6983. [PubMed: 17596446]
84. Strand AD, Baquet ZC, Aragaki AK, et al. Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration. J Neurosci 2007;27:11758–11768. [PubMed: 17959817]
85. Zuccato C, Liber D, Ramos C, et al. Progressive loss of BDNF in a mouse model of Huntington's disease and rescue by BDNF delivery. Pharmacol Res 2005;52:133–139. [PubMed: 15967378]
86. Dompierre JP, Godin JD, Charrin BC, et al. Histone deacetylase 6 inhibition compensates for the transport deficit in Huntington's disease by increasing tubulin acetylation. J Neurosci 2007;27:3571–3583. [PubMed: 17392473]
87. Hersch SM. Huntington's disease: prospects for neuroprotective therapy 10 years after the discovery of the causative genetic mutation. Curr Opin Neurol 2003;16:501–506. [PubMed: 12869810]
88. Yang W, Dunlap JR, Andrews RB, Wetzel R. Aggregated polyglutamine peptides delivered to nuclei are toxic to mammalian cells. Hum Mol Genet 2002;11:2905–2917. [PubMed: 12393802]
89. Schilling G, Savonenko AV, Klevytska A, et al. Nuclear-targeting of mutant huntingtin fragments produces Huntington's disease-like phenotypes in transgenic mice. Hum Mol Genet 2004;13:1599–1610. [PubMed: 15190011]

90. Boutell JM, Thomas P, Neal JW, et al. Aberrant interactions of transcriptional repressor proteins with the Huntington's disease gene product, huntingtin. Hum Mol Genet 1999;8:1647–1655. [PubMed: 10441327]
91. Dunah AW, Jeong H, Griffin A, et al. Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. Science 2002;296:2238–2243. [PubMed: 11988536]
92. Holbert S, Denghien I, Kiechle T, et al. The Gln-Ala repeat transcriptional activator CA150 interacts with huntingtin: neuropathologic and genetic evidence for a role in Huntington's disease pathogenesis. Proc Natl Acad Sci U S A 2001;98:1811–1816. [PubMed: 11172033]
93. Nucifora FC Jr, Sasaki M, Peters MF, et al. Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 2001;291:2423–2428. [PubMed: 11264541]
94. Steffan JS, Bodai L, Pallos J, et al. Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. Nature 2001;413:739–743. [PubMed: 11607033]
95. Steffan JS, Kazantsev A, Spasic-Boskovic O, et al. The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proc Natl Acad Sci U S A 2000;97:6763–6768. [PubMed: 10823891]
96. McCampbell A, Taylor JP, Taye AA, et al. CREB-binding protein sequestration by expanded polyglutamine. Hum Mol Genet 2000;9:2197–2202. [PubMed: 10958659]
97. Sadri-Vakili G, Bouzou B, Benn CL, et al. Histones associated with downregulated genes are hypo-acetylated in Huntington's disease models. Hum Mol Genet 2007;16:1293–1306. [PubMed: 17409194]
98. Stack EC, Del Signore SJ, Luthi-Carter R, et al. Modulation of nucleosome dynamics in Huntington's disease. Hum Mol Genet 2007;16:1164–1175. [PubMed: 17403718]
99. Kazantsev AG, Hersch SM. Drug targeting of dysregulated transcription in Huntington's disease. Prog Neurobiol 2007;83:249–259. [PubMed: 17379386]
100. Sadri-Vakili G, Cha JH. Mechanisms of disease: Histone modifications in Huntington's disease. Nat Clin Pract Neurol 2006;2:330–338. [PubMed: 16932577]
101. Butler R, Bates GP. Histone deacetylase inhibitors as therapeutics for polyglutamine disorders. Nat Rev Neurosci 2006;7:784–796. [PubMed: 16988654]
102. DiFiglia M, Sena-Esteves M, Chase K, et al. Therapeutic silencing of mutant huntingtin with siRNA attenuates striatal and cortical neuropathology and behavioral deficits. Proc Natl Acad Sci U S A 2007;104:17204–17209. [PubMed: 17940007]
103. Denovan-Wright EM, Davidson BL. RNAi: a potential therapy for the dominantly inherited nucleotide repeat diseases. Gene Ther 2006;13:525–531. [PubMed: 16237462]
104. Miller TW, Messer A. Intrabody applications in neurological disorders: progress and future prospects. Mol Ther 2005;12:394–401. [PubMed: 15964243]
105. Coufal M, Maxwell MM, Russel DE, et al. Discovery of a novel small-molecule targeting selective clearance of mutant huntingtin fragments. J Biomol Screen 2007;12:351–360. [PubMed: 17379859]
106. Valera AG, Diaz-Hernandez M, Hernandez F, Ortega Z, Lucas JJ. The ubiquitinproteasome system in Huntington's disease. Neuroscientist 2005;11:583–594. [PubMed: 16282599]
107. Brignull HR, Morley JF, Morimoto RI. The stress of misfolded proteins: C. elegans models for neurodegenerative disease and aging. Adv Exp Med Biol 2007;594:167–189. [PubMed: 17205684]
108. Ferrante RJ, Andreassen OA, Dedeoglu A, et al. Therapeutic effects of coenzyme Q10 and remacemide in transgenic mouse models of Huntington's disease. J Neurosci 2002;22:1592–1599. [PubMed: 11880489]
109. Andreassen OA, Dedeoglu A, Ferrante RJ, et al. Creatine increase survival and delays motor symptoms in a transgenic animal model of Huntington's disease. Neurobiol Dis 2001;8:479–491. [PubMed: 11447996]
110. Ferrante RJ, Andreassen OA, Jenkins BG, et al. Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. J Neurosci 2000;20:4389–4397. [PubMed: 10844007]
111. Andreassen OA, Ferrante RJ, Huang HM, et al. Dichloroacetate exerts therapeutic effects in transgenic mouse models of Huntington's disease. Ann Neurol 2001;50:112–117. [PubMed: 11456300]

112. Andreassen OA, Ferrante RJ, Dedeoglu A, Beal MF. Lipoic acid improves survival in transgenic mouse models of Huntington's disease. Neuroreport 2001;12:3371–3373. [PubMed: 11711888]
113. Chen M, Ona VO, Li M, et al. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nat Med 2000;6:797–801. [PubMed: 10888929]
114. Dedeoglu A, Kubilus JK, Jeitner TM, et al. Therapeutic effects of cystamine in a murine model of Huntington's disease. J Neurosci 2002;22:8942–8950. [PubMed: 12388601]
115. Karpuj MV, Garren H, Slunt H, et al. Transglutaminase aggregates huntingtin into nonamyloidogenic polymers, and its enzymatic activity increases in Huntington's disease brain nuclei. Proc Natl Acad Sci U S A 1999;96:7388–7393. [PubMed: 10377424]
116. Nguyen T, Hamby A, Massa SM. Clioquinol down-regulates mutant huntingtin expression in vitro and mitigates pathology in a Huntington's disease mouse model. Proc Natl Acad Sci U S A 2005;102:11840–11845. [PubMed: 16087879]
117. Youdim MB, Stephenson G, Ben Shachar D. Ironing iron out in Parkinson's disease and other neurodegenerative diseases with iron chelators: a lesson from 6-hydroxydopamine and iron chelators, desferal and VK-28. Ann N Y Acad Sci 2004;1012:306–325. [PubMed: 15105275]
118. Landwehrmeyer GB, Dubois B, de Yebenes JG, et al. Riluzole in Huntington's disease: a 3-year, randomized controlled study. Ann Neurol 2007;62:262–272. [PubMed: 17702031]
119. Rosas HD, Koroshetz WJ, Jenkins BG, et al. Riluzole therapy in Huntington's disease (HD). Mov Disord 1999;14:326–330. [PubMed: 10091628]
120. Duan W, Guo Z, Jiang H, et al. Paroxetine retards disease onset and progression in Huntingtin mutant mice. Ann Neurol 2004;55:590–594. [PubMed: 15048901]
121. Hockly E, Richon VM, Woodman B, et al. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, ameliorates motor deficits in a mouse model of Huntington's disease. Proc Natl Acad Sci U S A 2003;100:2041–2046. [PubMed: 12576549]
122. Ferrante RJ, Kubilus JK, Lee J, et al. Histone deacetylase inhibition by sodium butyrate chemotherapy ameliorates the neurodegenerative phenotype in Huntington's disease mice. J Neurosci 2003;23:9418–9427. [PubMed: 14561870]
123. Ferrante RJ, Ryu H, Kubilus JK, et al. Chemotherapy for the brain: the antitumor antibiotic mithramycin prolongs survival in a mouse model of Huntington's disease. J Neurosci 2004;24:10335–10342. [PubMed: 15548647]
124. Gardian G, Browne SE, Choi DK, et al. Neuroprotective effects of phenylbutyrate in the N171-82Q transgenic mouse model of Huntington's disease. J Biol Chem 2005;280:556–563. [PubMed: 15494404]
125. Keene CD, Rodrigues CM, Eich T, Chhabra MS, Steer CJ, Low WC. Tauroursodeoxycholic acid, a bile acid, is neuroprotective in a transgenic animal model of Huntington's disease. Proc Natl Acad Sci U S A 2002;99:10671–10676. [PubMed: 12149470]
126. Zuccato C, Cattaneo E. Role of brain-derived neurotrophic factor in Huntington's disease. Prog Neurobiol 2007;81:294–330. [PubMed: 17379385]
127. Ranen NG, Peyser CE, Coyle JT, et al. A controlled trial of idebenone in Huntington's disease. Mov Disord 1996;11:549–554. [PubMed: 8866496]
128. Peyser CE, Folstein M, Chase GA, et al. Trial of d-alpha-tocopherol in Huntington's disease. Am J Psychiatry 1995;152:1771–1775. [PubMed: 8526244]
129. Safety and tolerability of the free-radical scavenger OPC-14117 in Huntington's disease. The Huntington Study Group. Neurology 1998;50:1366–1373. [PubMed: 9595988]
130. Tabrizi SJ, Blamire AM, Manners DN, et al. High-dose creatine therapy for Huntington disease: a 2-year clinical and MRS study. Neurology 2005;64:1655–1656. [PubMed: 15883340]
131. Hersch SM, Gevorkian S, Marder K, et al. Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. Neurology 2006;66:250–252. [PubMed: 16434666]
132. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. Neurology 2001;57:397–404. [PubMed: 11502903]
133. Dubinsky R, Gray C. CYTE-I-HD: phase I dose finding and tolerability study of cysteamine (Cystagon) in Huntington's disease. Mov Disord 2006;21:530–533. [PubMed: 16258942]

134. Puri BK, Leavitt BR, Hayden MR, et al. Ethyl-EPA in Huntington disease: a double-blind, randomized, placebo-controlled trial. Neurology 2005;65:286–292. [PubMed: 16043801]

135. Kremer B, Clark C, Hardy M, Almqvist E, Raymond L, Hayden M. Lamotrigine does not retard the progression of Huntington's disease. WFN Working Group on Huntington's Disease 1997:34.

136. Dosage effects of riluzole in Huntington's disease: a multicenter placebo-controlled study. Neurology 2003;61:1551–1556. [PubMed: 14663041]

137. Seppi K, Mueller J, Bodner T, et al. Riluzole in Huntington's disease (HD): an open label study with one year follow up. J Neurol 2001;248:866–869. [PubMed: 11697523]

TABLE 1

POTENTIAL NEUROPROTECTION TARGETS

Huntingtin production
Huntingtin cleavage into toxic fragments
Nuclear transport of huntingtin
Huntingtin misfolding
Huntingtin clearance
Huntingtin posttranslational modifications
Protein aggregation
Transcription factor/complex function
Chromatin regulation
Energetic abnormalities
Oxidative Stress
Synaptic stress
Cell death signaling
Autophagy
Proteosome dysfunction
Neurotrophin deficiencies