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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Photo kindly provided by John Hammond

Palm Springs: The surroundings of CHDI's 5th Annual Huntington's Disease Therapeutics Conference

FEATURE ARTICLE

By Simon Noble, CHDI Management/CHDI Foundation, New York, USA

Clinical Progression

CHDI's 5th Annual Huntington's Disease Therapeutics Conference: A Forum for Drug Discovery and Development was held in Palm Springs, California, from 8th to 11th February 2010

There were auspicious signs even before it began. Exciting news about a Phase III clinical trial of a potential new drug for Huntington's disease (HD) preceded the conference, and that clinical perspective continued as 215 participants gathered in Palm Springs. For the first time a full day of the conference was devoted to a clinical workshop, affirming that the HD research community now has at least one eye firmly fixed on translating their research findings from animal models into tangible therapies for the clinic.

Robert Pacifici of CHDI officially opened the conference, explaining that CHDI is a "foundation-funded, not-for-profit, virtual biotech company that is exclusively dedicated to finding therapies that delay the onset or slow the progression of HD," and that in addition to driving its own drug development projects also "acts as a collaborative enabler, which is the spirit of this conference," aiming to nurture the exchange of ideas and build productive partnerships.

Pacifici picked out three broad themes evident in this year's conference program. The first was a focus on "our most well-validated [therapeutic] target, huntingtin itself, both the gene and the protein." The second was experimental medicine, "learning from the patients; there's nothing more precious to a drug hunter than an observation made in the human population that we're aspiring to treat." The third was the maturation of the clinical pipeline, and "a set of emerging drug candidates that we're now talking about in terms of their readiness for clinical trials." >>

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By Simon Noble, CHDI Management/CHDI Foundation, New York, USA
March 2010 · Issue 09


John Hammond

Steven T. Seagle

Keynote address

This year's keynote speaker was Steven T. Seagle, an accomplished writer who works in comic books, television, film, theater, and animation. In his best known work, the graphic novel *It's a Bird…* (Vertigo Comics, 2004), he tells in semi-autobiography the story of his being offered the chance to write the Superman comic book whilst simultaneously struggling with HD diagnoses within his family and what that has meant in his life. His deeply-affecting but highly-entertaining speech contrasted the reality of the disabling HD with the fantasy of the hyper-abled Superman. HD is, he said, "part of my family's secret identity" and that "you can fear the unknown or you can accept the unknown… I chose to accept the unknown a long time ago."

Disease modification

Half of the presentations during the clinical workshop day discussed disease modification. Most usually, clinical trials of drug candidates aim to improve a specific clinical symptom, for example voluntary motor function. But disease modification is another potential type of clinical trial endpoint that would aim to change the underlying disease pathophysiology, not necessarily a specific clinical sign. Biomarkers will be required to track disease progression and need to be linked to improved clinical outcome with experimental evidence. Since regulatory authorities are mandated to take a conservative approach, the HD research community needs to show clearly that some of these biomarkers do consistently lead to improved disease course.

One key issue is that treating pre-manifest HD patients will have to rely on surrogate biomarkers since overt physical symptoms are not yet evident. Sarah Tabrizi of University College London is looking at volunteers enrolled in the TRACK-HD study of pre-manifest and early HD to measure changes in disease over relatively short time periods. She is seeing some quite marked changes in various motor functions that could correlate to significant atrophy in brain regions within only a year, which would enable much more sensitive measurement of disease progression.

The Food and Drug Administration (FDA) has recently set up a working group to look at disease modification criteria in Alzheimer's disease and will soon do the same for HD. Cristina Sampaio of the European Medicines Agency (EMEA) said that "validating a surrogate endpoint is, I must say, a daunting task," but, unlike the FDA, the EMEA does offer a two-step approval where the primary endpoint can be disease modification with a secondary clinical endpoint of delay of disability.

Phase III trial

There was a buzz around the conference in anticipation of Joakim Tedroff's presentation, not only for the good news this may be for HD patients but also for the boost it gives to the research community as they continue their efforts to develop other effective drugs. Tedroff from NeuroSearch presented encouraging preliminary results from the EHDN randomized, double-blind MermaiHD Phase III clinical trial in HD patients of ACR16 (pridopidine, trade name Huntexil®), a dopaminergic stabilizer that in animal models seems to beneficially affect motor function, cognitive impairment and psychosis. The trial data indicates that ACR16 modestly (but statistically significantly) improved both voluntary motor function, the trial's primary endpoint, and involuntary motor function. Importantly, the drug was well tolerated with no increase in adverse events and no worsening of disease signs or symptoms. These results have prompted cautious optimism that ACR16 could be valuable as an HD therapy.

Targeting huntingtin

Reducing the levels of mutant huntingtin in the brain is a potential therapeutic approach that will very likely modify HD onset and progression, but the technical challenges are considerable and the possible side effects unknown. One tricky question is just how much normal huntingtin does a healthy animal need, since the protein's functions are still not entirely understood but it is clearly essential throughout development; this question becomes critical if researchers find a way to reduce both mutant and normal huntingtin as a therapeutic approach. Andrea Kudwa from PsychoGenics Inc. described the development of a huntingtin knockdown mouse model that aims to shed light on this issue. Don Cleveland of the University of California described how antisense oligonucleotides can be used to decrease mutant and normal huntingtin levels in HD mouse models with beneficial consequences. To avoid reducing normal huntingtin,


Gene Veritas

Don Lo and Robin Meray

By Simon Noble, CHDI Management/CHDI Foundation, New York, USA

Neil Aronin of the University of Massachusetts showed that RNA interference could be specifically targeted to the mutant mRNA. The technology to deliver these classes of therapeutics to the brain has yet to be developed and Dinah Sah from Alnylam showed encouraging progress in delivery to specific brain regions.

Improving animal models

There were a host of presentations describing new animal models of HD and improved methods of phenotyping. George Rebec of Indiana University views HD as "a communication problem between neurons," and he has shown that there is a clear lack of coordination in neuronal firing in HD mouse and rat models that is reflected in their lack of limb coordination. Dani Brunner of PsychoGenics Inc. described their futuristic automated system that exhaustively monitors mouse colony behaviour and uses computer modeling to distinguish the behaviours of individual mice that could serve as a much more sensitive set of markers to test therapeutic interventions for HD. And Jenny Morton of the University of Cambridge is characterizing a transgenic sheep HD model that, due to their large size, could be useful in testing delivery of novel classes of drugs and may allow measurement of motor, cognitive, and possibly even psychiatric symptoms.

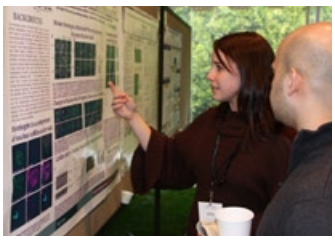
Jenny Morton

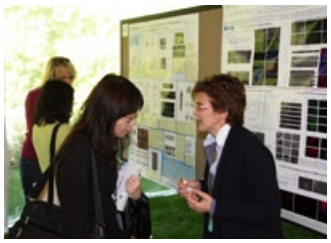
Huu Phuc Nguyen

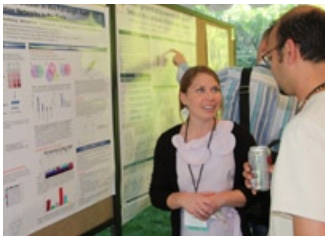
This year's poster prize winner was Huu Phuc Nguyen of the University of Tuebingen for generating a transgenic rat that expresses mutant human huntingtin and exhibits early progressive motor deficits, impaired motor skill learning, and reduced activity. Rats have much better learning abilities than mice, so any subtle cognitive changes due to the mutant huntingtin could be more easily measurable.

Awards ceremony

The poster awards were presented by intrepid roving reporter and indefatigable HD patient advocate Charles Sabine, who was on hand throughout the conference with a camera crew. Charles' film report of the conference, 'Postcard from Palm Springs,' will be posted at the HDSA and EHDN websites. Charles said he has made it his mission to help HD-affected families overcome their fears of confronting the disease so that they can better support research efforts, particularly clinical trials. "That task is made a lot easier by the fact that I can look all of those people in the eye and tell them, with sincerity and certainty, of the commitment that is so evident at this meeting, and which gives them the chance to dare to hope."







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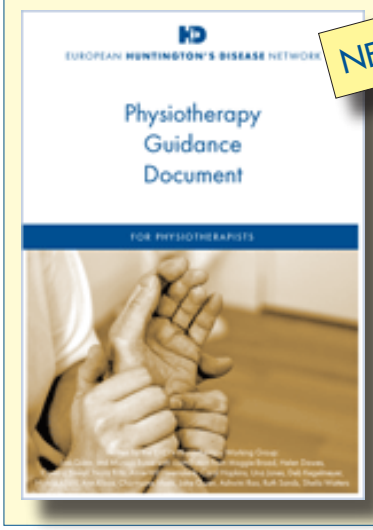


NEW

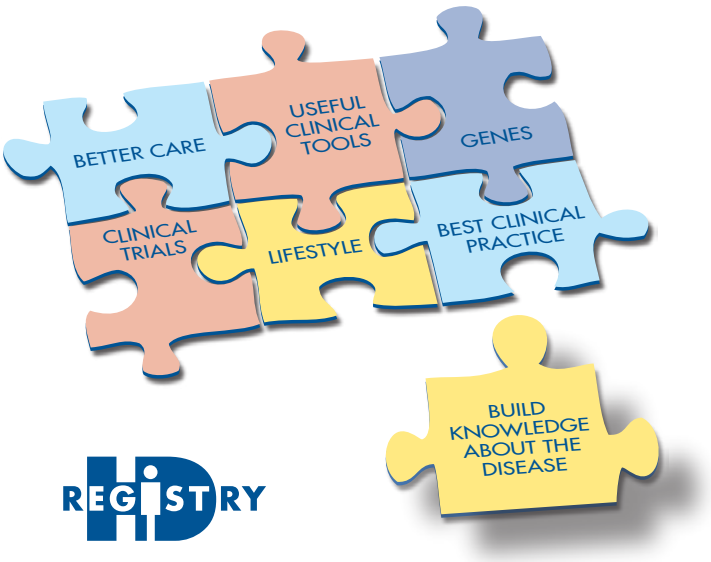
Physiotherapy Guidance Document

Physiotherapy is becoming more frequently recommended for people with Huntington's Disease (HD) but to date, there have been no specific implementation guidelines. The Physiotherapy Working Group of the EHDN has developed a comprehensive Guidance Document for Physiotherapists. It aims to assist therapists in implementing a plan of care that is consistent with current best practice in physiotherapy provision to people at all stages of HD. The document will be reviewed and updated as new research becomes available.

The current version (180 pages, February 2010) is freely available for download at https://www.euro-hd.net/html/network/groups/physio.

REGISTRY's Cognitive Sub-Studies

REGISTRY version 2.0 assesses cognitive function using the UHDRS Cognitive Assessment (Stroop, Symbol Digit Modalities Test, and Letter Fluency). This assessment takes 15 minutes to administer and shows sensitivity to cognitive change over time. However, the tests are restricted to measures of psychomotor speed, attention, and executive functions. In an effort "to develop a battery of a variety of tests selected on the basis of their proven sensitivity to longitudinal change and potential utility in clinical trials", the Cognitive Phenotype Working Group (CPWG) has defined the EHDN Full Neuropsychological Assessment. This consists of the UHDRS Cognitive Assessment, Category Fluency, Trail Making Parts A & B, Hopkins Verbal Learning Test, and the Mattis Dementia Rating Scale. An accompanying manual harmonises guidelines for administration and scoring.



Tools and goals used by REGISTRY as part of the worldwide collaboration to find treatments for Huntington's disease.

Crucially, cross-cultural normative data on cognitive measures is lacking. Therefore, the CPWG has proposed the "Normative Cognitive Data" sub-study to collect cognitive performance data in a European-based control population. Establishing normative values will provide the standard against which an individual's cognitive scores can be compared, therefore strengthening the interpretation of task performance. It will also enable conclusions to be drawn about the extent to which cross-cultural differences influence cognitive performance.

The Full Neuropsychological Assessment is not exhaustive and it is recognised that additional cognitive tests may be useful as complementary outcome measures in clinical trials. Therefore, the CPWG is exploring two additional cognitive tests under the sub-study framework: the Montreal Cognitive Assessment (MoCA) and the Syntax Test.

The MoCA is a brief measure of global cognitive ability. This sub-study seeks to obtain cross-cultural data to determine its robustness as a measure for detecting 'global' cognitive change in HD. If the MoCA is found to be a reliable outcome measure, it could be used in clinical trials assessing the efficacy of so-called 'cognitive enhancers' in HD.

The Syntax Test (developed by Anne-Catherine Bachoud-Lévi and Marc Teichmann) focuses on language ability, a cognitive function traditionally thought to be relatively unimpaired in HD. Specifically, this task measures syntactic processing (the means by which humans are able to use linguistic knowledge to create sentences). Preliminary findings indicate task sensitivity in discriminating between 'very early' and 'early' stages of the disease. The first phase of this sub-study seeks to replicate these findings in French- and English-speaking HD populations. If this aim is met, a second phase will further examine its application across a wider range of European languages.

The portfolio of cognitive sub-studies underlines the clear progress made by the CPWG in reaching its goals: to develop a neuropsychological battery to be used in REGISTRY; to improve standardisation of neuropsychological test administration in order to increase data reliability; and to develop novel assessment tools and evaluate their sensitivity to the progression of HD for potential use as outcome measures in therapeutic trials. It is hoped that through the REGISTRY sub-studies a crucial step will be achieved in expediting data collection that is central to development of robust, reliable, and sensitive cognitive outcome measures.

Environmental Modifiers Working Group

Kaye Trembath & Martin Delatycki (Melbourne, Australia) and Monica Busse-Morris (Cardiff, UK)

Studies using mouse models of Huntington's disease (HD) have shown that rearing mice in an enriched environment delays the onset of some symptoms. In other neurodegenerative disorders such as Alzheimer's and Parkinson's diseases, symptom onset can also be influenced by the type and level of activity regularly undertaken prior to the development of the disease. Such findings raised the possibility that lifestyle in the pre-symptomatic phase may also affect age-at-onset in HD. A retrospective study of 154 individuals, conducted in Australia and New Zealand, has shown that avoiding a passive lifestyle may well delay the onset of symptoms of HD.

Bad plan for those at-risk of HD

Aims

The ultimate aim of this working group is to identify potential lifestyle strategies that, if employed by at-risk individuals from an early age, could delay the onset of their symptoms. Substantiating the Australasian findings is the first step in this process.

Current projects

• **Retrospective study 2** – This is a follow-up to the original study and aims to examine the impact of pre-symptomatic lifestyle on age-at-onset of HD. It involves a single, short (20-30 minute), semi-structured interview to gather data relating to pre-symptomatic lifestyle history. Study participants must be aged 18 years or older with a diagnosis of HD confirmed by a neurologist, a mutation of known CAG repeat length in the *HTT* gene, and be judged (by a qualified professional) to be capable of responding to an interview in a meaningful manner. They should preferably (but not necessarily) be accompanied by a family member, and will be recruited through EHDN study sites commencing early in 2010. The interview will be an optional module within REGISTRY version 3.

• **Development of a prospective study** – The working group is developing a detailed prospective study that will determine which specific lifestyle factors can actually be measured. It will also examine whether or not modification of such lifestyle factors can be effective in producing a change in mean age-at-onset. The ultimate aim of our project is to provide those at risk of HD with early (perhaps childhood) lifestyle interventions that may delay the onset of their disease. The retrospective studies are being used to guide the development of the prospective study.

This phase of the project will involve participants who are 'at risk' of HD, but yet asymptomatic. We plan to monitor, over time, a range of environmental factors and lifestyle activities that may affect age-at-onset. In the future, it may also be feasible to investigate the impact of environmental factors on the progression of the disease in symptomatic HD patients.

For further information please contact Monica Busse-Morris (BusseME@cardiff.ac.uk), Kaye Trembath (kaye.trembath@ghsv.org.au) or Martin Delatycki (martin.delatycki@ghsv.org.au).

Functional Ability Working Group

Aileen Ho (Reading, UK)

What is functional ability and why is it important?

In Huntington's disease (HD) patients, gradual changes in motor control, mental ability, mood and personality eventually lead to a loss of independence. Deterioration in these different domains does not occur discretely. Rather, they interact to affect negatively a person's ability to handle their usual everyday activities. As HD develops, individuals experience deterioration in their ability to perform day-to-day activities, such as going to work, organising the family's activities, completing chores, handling finances and running the home. At a more elementary level, activities related to personal care and hygiene also become more difficult. Any change in the ability to perform these real-world activities can have a large impact on independence and the well-being of a patient. Therefore clinical regulatory bodies are increasingly interested in the impact of disease on these functional abilities, since they have clear and meaningful implications for people's quality of life. The accurate evaluation of functional ability is also important in terms of patient management and care.

Rationale and Aim

A key objective of the Functional Ability Working Group is to develop suitable means of assessing functional ability in HD. The scales currently used to measure functional ability do not capture the full impact of the disease over its duration. A better functional assessment will lead to a more comprehensive understanding of changes in functional ability over time and of the means by which these might be improved.

Activities

Over the past year we have developed close links with the Standard of Care Working Group in their initiative to provide 'best practice' guidelines. We have engaged in mutually beneficial exchanges to review areas such as communication, language, speech and swallowing function. We are working towards providing a seamless link between current recommended practice and the development of evidence-based practice.

We are expanding the functional assessment scales that are currently in use within EHDN. The Total Functional Assessment Scale provides a wider coverage of activities compared to the Total Capacity Scale, but allows only for binary (yes/no) responses. We are gathering pilot data on the usefulness of providing extended response options for the Total Functional Assessment Scale.

We plan to investigate areas of function that are not fully covered by current assessment methods, such as speech and communication. We have already gathered preliminary data that will inform further development of the Assessment Scale. We shall also directly assess task performance, using measures for assessment of function, rather than relying on self and/or carer reports.

Group membership and meetings

The Functional Ability Working Group has representatives from the UK, Sweden, Finland, Germany, Spain, Italy, the Netherlands, and USA. The group consists of people with interdisciplinary skills who meet approximately twice a year. We are united by a common interest in how people across the spectrum of HD function outside of the clinic in their daily life. We invite researchers, statisticians, clinicians and allied health professionals (e.g. occupational therapists, speech therapists, specialist nurses, support workers, etc) with similar interests to join us. If you are interested, please contact Aileen Ho (a.k.ho@reading.ac.uk).

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
March 2010 · Issue 09

Motor abnormalities in premanifest persons with Huntington's disease: the PREDICT-HD study

Kevin M. Biglan et al., Movement Disorders (2009), 24: 1763-1772

Motor impairments detected with the UHDRS distinguish premanifest HD from control subjects and are associated with closer proximity to estimated disease diagnosis.

Background

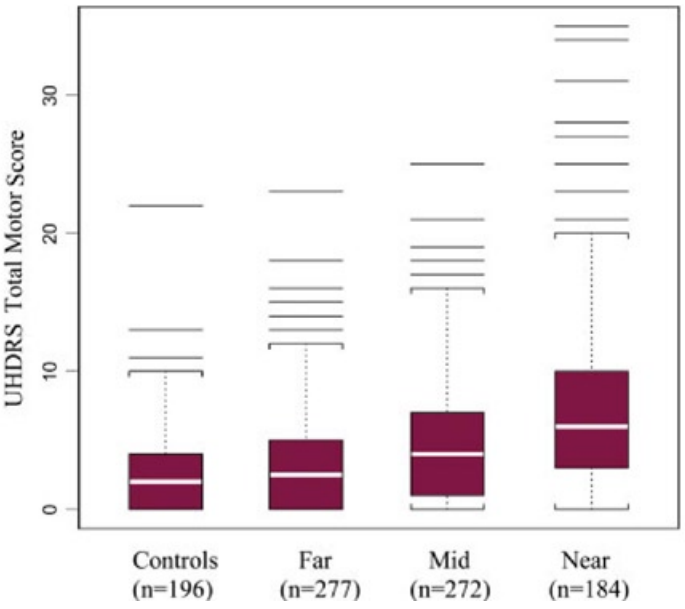
PREDICT-HD is an observational study of the Huntington Study Group aimed at identifying clinical and biological markers of Huntington's disease (HD) in premanifest gene mutation carriers. A previous publication reported small changes in clinical and neuroimaging parameters 15-20 years prior to predicted clinical diagnosis (see EHDN *News* Issue of March 2009). The present work focused on motor signs of HD, establishing a relationship between motor function, probability of diagnosis and striatal volume.

Subjects and methods

Subjects were 733 premanifest HD gene mutation carriers with diagnostic confidence ≤ 3 in the UHDRS[1]. Cases were divided into three groups: far (> 15 years), mid (9 to 15 years) and near (< 9 years) to estimated clinical diagnosis according to the CAG- and age-based predictive model of Langbehn et al. (Clin Genet 2004, 65: 267-277). Control subjects were 196 individuals who had tested negative for the HD mutation. Motor signs were assessed with the UHDRS Motor Scale. Striatal volumes (as percentage of whole-brain volumes) were calculated from 1.5 Tesla MRI[2] scans. Comparisons between cases and controls were performed using *t*-tests and Chi-square tests. Linear regression models assessed the relationship between total motor scores, motor domain scores or individual motor items and estimated diagnosis probability or striatal volume.

Results

Subjects had worse UHDRS total motor scores, worse motor domain scores and smaller striatal volumes than controls ($P < 0.0001$ for all). Worse total motor scores ($P < 0.0001$), worse motor domain scores ($P \leq 0.001$ for all domains, except rigidity) and greater striatal atrophy ($P < 0.001$) were associated with closer proximity to estimated diagnosis. From the five motor domains of UHDRS (bradykinesia, chorea, dystonia, oculomotor and rigidity), bradykinesia and chorea were significantly associated with probability of diagnosis. Oculomotor signs were the third most important domain, but failed statistical significance. Single motor item analysis revealed that worse scores on finger tapping, tandem gait, Luria[3], saccade initiation and chorea are associated with a greater probability of diagnosis.



UHDRS Total Motor Scores in controls and cases by proximity to diagnosis. Box = 25-75% range; horizontal lines = outlying individual values.

Worse total motor scores also correlated with smaller striatal volumes ($P < 0.0001$). Stronger striatal atrophy was significantly associated with worse scores on the bradykinesia, chorea and oculomotor domains. Assessments of saccade velocity, finger tapping, tandem gait, chorea and tongue protrusion identified these items as significantly associated with smaller striatal volumes.

Conclusions

These findings suggest that the UHDRS motor examination may be a useful outcome measure in clinical trials aimed at delaying disease onset in premanifest HD. Longitudinal follow-up will be necessary to better determine which motor domains and items are sensitive to change over time.

[1] Unified Huntington's Disease Rating Scale
[2] Magnetic Resonance Imaging
[3] fist-edge-palm test

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
March 2010 · Issue 09

Two studies paving the way to allele-specific RNA interference therapy for Huntington's disease

A majority of Huntington's disease patients may be treatable by individualized allele-specific RNA interference

Maria S. Lombardi et al., Experimental Neurology (2009), 217: 312-319

Five siRNAs targeting three SNPs may provide therapy for three-quarters of Huntington's disease patients

Edith L. Pfister et al., Current Biology (2009), 19: 774-778

Background

RNA interference has been contemplated as a potential treatment for Huntington's disease (HD) based on the suppression of the production of mutant huntingtin (HTT) in susceptible brain regions. Potentially, this can be achieved by delivery to the brain of either a small interfering RNA (siRNA), or DNA encoding a functionally equivalent short hairpin RNA (shRNA) that will target *HTT* mRNA. In either instance, the molecule used must distinguish between the normal and mutant *HTT* allele. As the activity of siRNA is highly specific, a single mismatch between the siRNA and the target mRNA may be sufficient to reduce the interference effect. Hence, if an siRNA is targeted to a portion of mRNA containing the site of a single nucleotide polymorphism (SNP) within the *HTT* gene, the treatment may discriminate between the normal and mutant *HTT* alleles. This strategy was successfully demonstrated in culture of fibroblasts derived from an HD patient (see EHDN *News* Issue of September 2008). However, for this therapeutic approach to be clinically feasible, it is crucial to determine which polymorphic sites are the most promising for an allele-specific therapy and what proportion of HD patients could be treated using the same siRNA molecules.

Results

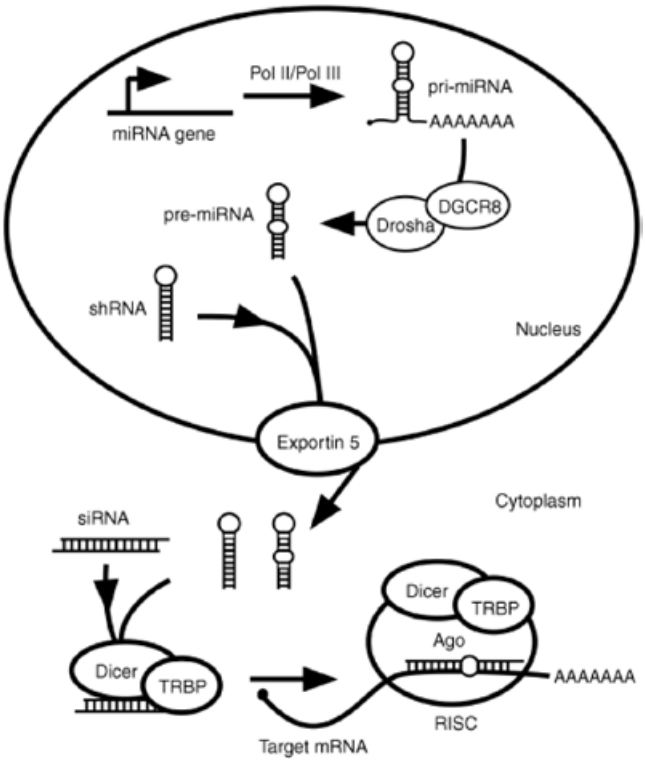
Lombardi et al. studied 327 unrelated HD patients selected from a cohort of 875 Caucasian patients of the Institute Carlo Besta (Milan, Italy). Genomic DNA was extracted from lymphocytes and genotyped at 26 polymorphic sites in the *HTT* gene which were selected according to specific criteria. 282 patients (86.2%) were heterozygous for at least one site of these 26 SNPs. A list of all possible combinatorial subsets comprised of one or more SNPs was generated. This analysis revealed that 46.2% of the patients in this cohort could be treated with an siRNA targeting one SNP and 85.6% with siRNAs targeting 7 SNPs.

Pfister et al. sequenced 22 predicted SNP sites in the *HTT* gene from 109 HD patients and 116 control subjects. 48.6% of the HD cohort was heterozygous at a single SNP site, and one isoform of this SNP was significantly associated with HD, comprising 26% of the *HTT* alleles in patients but only 6% in controls. Eight other SNP sites were each heterozygous in > 33% of the patient population, but did not show a statistically significant association with HD. The authors found that five allele-specific siRNAs, corresponding to just three SNP sites, could cover 75% of this HD population.

Conclusions

These studies demonstrate that a relatively small number of allele-specific siRNAs could provide effective RNA interference therapy for the majority of European and US American HD patients.

Allele is one of the two copies of each gene or genetic marker in organisms with two sets of chromosomes. Single nucleotide polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide in the genome differs between chromosomes.



The RNA interference pathway

Summary by Diana Raffelsbauer, PharmaWrite, Giebelstadt, Germany
March 2010 · Issue 09

Intrabody gene therapy ameliorates motor, cognitive, and neuropathological symptoms in multiple mouse models of Huntington's disease

Amber L. Southwell et al., Journal of Neuroscience (2009), 29: 13589-13602

Intrabody against mutant huntingtin proves beneficial in five mouse models of Huntington's disease.

Background

A promising approach to preventing neuronal loss in Huntington's disease (HD) is the use of intrabodies (iAbs) that bind to mutant huntingtin (mHTT). Intrabodies are recombinant antibody fragments delivered into cells by means of viruses. A number of anti-HTT iAbs have been created. Among them, Happ1 and V_L12.3 were shown to reduce toxicity of mHTT fragments in cell culture and brain slice models of HD (see EHDN *News* Issue of June 2009). This study tested the therapeutic potential of these two iAbs in a lentiviral model and four transgenic mouse models of HD.

Materials and methods

The lentiviral model was created by injecting C57BL/6 mice with a virus encoding a mHTT fragment (mHDx-1Q103). Transgenic HD mice were R6/2 and N171-82Q (which produce N-terminal mHTT fragments) as well as YAC128 and BACHD (which produce full-length mHTT). These models behave similarly in most aspects of the HD phenotype (motor impairments, cognitive deficits, weight loss, survival, HTT aggregation, striatal atrophy and loss of medium spiny neurones). Domains assessed were motor function (rotarod, beam crossing, climbing, clasping and amphetamine-induced rotation), behaviour – in particular anxiety (open field test), cognition (novel object location and preference tests) and brain pathology (histology).

Results

The outcomes of the treatment with Happ1 are shown in the table below. In summary, Happ1 treatment improved motor, behavioural and cognitive performance in transgenic HD models. In addition, Happ1 prevented striatal neurone loss in the lentiviral model, reduced HTT aggregation in the lentiviral and R6/2 models and normalised ventricle size in the R6/2, YAC128 and BACHD mice. While Happ1 had no effect on R6/2, YAC128 or BACHD body weight or R6/2 survival, it significantly increased both body weight and life span of N171-82Q mice. Although V_L12.3 treatment improved behaviour and neuropathology in the lentiviral model, it showed either no effect or adverse effects in the transgenic mice.

Assay	Outcome	Models assessed
Rotarod	improved	R6/2, N171-82Q, YAC128 and BACHD
Beam crossing	improved	R6/2, N171-82Q, YAC128 and BACHD
Climbing	improved	YAC128 and BACHD
Clasping	improved	N171-82Q
Amphetamine-induced rotation behaviour	prevented*	lentiviral model
Open field behaviour (anxiety)	normalised	YAC128 and BACHD
Learning (spatial and cortical)	improved in YAC128; no effect in BACHD	YAC128 and BACHD
Loss of MSNs[1]	prevented*	lentiviral model
Mutant HTT aggregation	reduced*	lentiviral model and R6/2
Ventricle size (atrophy)	reduced	R6/2, YAC128 and BACHD
Body weight	improved in N171-82Q; no effect in the other models	R6/2, N171-82Q, YAC128 and BACHD
Survival	increased in N171-82Q; no effect in R6/2**	R6/2 and N171-82Q

[1] Medium spiny neurones

*Similar results were obtained with V_L12.3.

**V_L12.3 decreased survival of R6/2 mice.

Conclusions

Happ1 seems to reduce mHTT toxicity by increasing clearance of the mutant but not the wild-type protein. The beneficial effects of Happ1 treatment shown here suggest that strategies targeting the specific degradation of mHTT may represent a selective and effective therapy for HD with a low probability of off-target effects.

Upcoming Meetings 2010

Mar 06-10	41st Annual Meeting of the American Society for Neurochemistry, Santa Fe, NM, USA http://asneurochem.org/2010Meeting/ASN2010.htm
Mar 10-13	25th International Conference of Alzheimer's Disease, Thessaloniki, Greece http://www.adi2010.org/default.aspx
Mar 13	Environmental Modifier Working Group Meeting, London, UK https://www.euro-hd.net/html/network/news
Mar 26-27	Behavioural Phenotype Working Group Meeting, Birmingham, UK https://www.euro-hd.net/html/network/news
Mar 29-30	Cognitive Phenotype Working Group Meeting, Manchester, UK https://www.euro-hd.net/html/network/news
Apr 02	French Investigator Meeting, Venue to be announced, France https://www.euro-hd.net/html/network/news
Apr 10-17	2010 Annual Meeting of the American Academy of Neurology, Toronto, Canada http://www.aan.com/go/am10
Apr 22-23	Scottish and Irish Investigator Meeting, Aberdeen, UK https://www.euro-hd.net/html/network/news
Apr 22	Retirement Symposium for Sheila Simpson, Aberdeen, UK https://www.euro-hd.net/html/network/news
May 04-05	Scandinavian Investigator Meeting, Venue to be announced, Copenhagen, Denmark https://www.euro-hd.net/html/network/news
May 06-07	Genetic Testing and Counselling Working Group Meeting, Venue to be announced https://www.euro-hd.net/html/network/news
May 15	Parkinson Study Group/Huntington Study Group Symposium, Irving, TX, USA http://www.huntington-study-group.org/NewsEvents/EventsUpcomingMeetings/PS-GHSGSymposium/tabid/89/Default.aspx
May 17-21	Australian and New Zealand Association of Neurologists, Annual Scientific Meeting, Melbourne, Australia http://www.anzan2010.com/
June 13-17	14th International Congress of Parkinson's Disease and Movement Disorders, Buenos Aires, Argentina http://www.movementdisorders.org/congress/congress10/
Jun 19-23	20th Meeting of the European Neurological Society, Berlin, Germany http://www.congrex.ch/ens2010/
June 24	Biomarkers Working Group Meeting, Lund, Sweden https://www.euro-hd.net/html/network/news
June 25-27	National Convention of the Huntington's Disease Society of America, Raleigh, NC, USA http://www.hdsa.org/events/index.html?month=6&year=2010
Aug 8	Biological Modifiers Working Group Meeting, Boston, MA, USA https://www.euro-hd.net/html/network/news
Aug 28-Sept 1	23rd Congress of the European College of Neuropsychopharmacology, Amsterdam, The Netherlands http://www.ecnp.eu/emc.asp?pageId=1516
Sept 2	Quality of Life Working Group Meeting, Prague, Czech Republic https://www.euro-hd.net/html/network/news
Sept 3-5	6th Bi-Annual Plenary Meeting of the European Huntington's Disease Network, Prague, Czech Republic https://www.euro-hd.net/html/ehdn2010
Sept 5-6	13th Bi-Annual Meeting of the European Huntington Association, Prague, Czech Republic
Sept 25-28	14th Congress of the European Federation of Neurological Societies, Geneva, Switzerland http://efns2010.efns.org/
Oct 23-24	Convention of the German Huntington Help, 40th Anniversary of the German Huntington Self-Support Group, Duderstadt, Germany
Nov 13-17	40th Annual Meeting of the Society for Neuroscience, San Diego, CA, USA http://www.sfn.org/am2010/