July 2012 · Issue 16

EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Photos kindly provided by Lev Blumenstein and Gill Bates

At the Palm Springs Therapeutics Conference 2012

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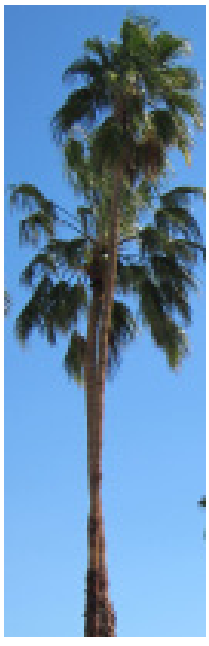
FEATURE ARTICLE

2012 HD Therapeutics Conference

Ed Wild, University College London, UK & Jeff Carroll, Western Washington University, USA

Palm Springs provided the backdrop to the 2012 Huntington's Disease Therapeutics Conference. Hosted by CHDI, the Conference brought together many of the world's top HD researchers to discuss the latest research and form valuable partnerships.



Systems Biology

The Conference began with a focus on **Systems Biology** (a term used to convey the idea that everything, from molecules and cells to communities, is connected). **Keith Elliston** (CHDI Vice President for Systems Biology) aims to apply the Systems Biology approach to maximize the work of HD scientists.

Lee Hood (Institute for Systems Biology, Seattle), an expert in applying technology to disease, has recently become interested in HD. Hood's team is sequencing the whole genomes of HD families and is looking for DNA changes that may affect the age at which HD symptoms begin.

Jim Gusella reflected on his work aimed at identifying genes that affect the progression of HD. Gusella plans to apply analytical methods using the interconnections of genes, to get the most out of large genetic studies that are underway.

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Hanchuan Peng (Howard Hughes Medical Institute) showed one example of how Systems Biology can enhance our understanding of HD. He has produced detailed 3-dimensional maps of cell connections in *C. elegans*, the nematode worms that are useful tools in genetics research. These maps show how diseases or treatments might be studied in order to understand how they affect whole networks of cells.

Gene silencing

Gene-silencing drugs bind to the messenger RNA that is produced from the HD gene, thereby decreasing the production of the mutant protein. The idea behind this approach is that down-regulating mutant huntingtin might delay the onset of HD symptoms and/or allow HD-affected neurons to recover from toxicity that has already been invoked. Thus far, gene-silencing drugs appear to be effective and safe, and at least four teams are planning trials to test their safety and efficacy in HD patients.

Frank Bennett spoke on behalf of Isis Pharmaceuticals, a company that specialises in anti-sense oligonucleotide (ASO) gene-silencing drugs. An ASO is a single-stranded DNA-like molecule which, if administered into the cerebral spinal fluid, can penetrate the brain quite well. Therefore, Isis plans to inject the ASOs into spinal fluid via the base of the spine. The cortex and striatum are both areas of the brain that are affected in HD. A trial in monkeys of one of the ASOs made by Isis showed that it reached various brain regions, especially the cortex and to a lesser extent the striatum. Human trials will tell us if this will be enough to improve symptoms in HD patients. Importantly, the drug appeared to be safe in the monkeys. Safety trials in animals are a crucial step on the way to trials in patients.

Neil Aronin of the University of Massachusetts is interested in testing gene therapy using sheep rather than monkeys. Sheep's large brains are ideal for refining the scanning and surgery techniques that will be needed for human gene-silencing trials. Aronin discussed how an RNA interference drug could switch off genes other than *HTT*. The need to design drugs that minimize these 'off-target' effects was highlighted by **Bev Davidson** (University of Iowa), who has performed very careful work to maximise their specificity.

Medical technology company Medtronic has published some of the most advanced results in HD gene silencing. **Bill Kaemmerer** reported that a trial of a gene-silencing drug in patients is in the advanced planning stage.

Steve Zhang (Sangamo BioSciences) spoke about gene silencing using 'zinc finger' drugs. These are drugs that attach directly to chosen sequences in DNA. If they can be targeted specifically to the HD gene, they could prevent it from being read and converted into the huntingtin protein, or even (although likely to be far in the future) snip out the mutant gene altogether.

Next-door neighbours

In order to treat HD effectively, many researchers believe that several treatments, targeting different problems in HD, may be necessary. So the session on 'upstream' and 'downstream' targets was important. Upstream and downstream targeting refers to the events before and after the huntingtin protein is made. The first step in making a protein involves creating an RNA 'message

molecule'. This mRNA manufacture is the 'upstream' process. After the protein is made, chemical tags are added that alter how the protein is handled in cells. This is known as post-translation modification and is the downstream process. Small changes to these processes might make a considerable difference to the detrimental effects of mutant huntingtin.

Melissa Moore (University of Massachusetts) explained how we might exploit the RNA-making machinery of the cell to treat HD. Drugs that work at the RNA level are already being tested in diseases like cystic fibrosis and are being considered as therapeutic approaches to HD.

Naoko Tanese (New York University) has found that the huntingtin protein associates with mRNA molecules made from many genes, raising the possibility that one function of huntingtin might be 'shuttling' RNA around cells.

Turning to the 'downstream' pathways, **Lisa Ellerby** (Buck Institute for Aging) reviewed the modifier tags that can be added to various parts of the huntingtin protein. She also discussed what is known about the enzymes that add and remove each tag.

How do we know which tags and enzymes are most important? **Marcy MacDonald** (Massachusetts General Hospital) has been using a genetics-based approach to tag identification. Her work has provided insights into the structure of the huntingtin protein and how it might form interactions with other proteins.

Dimitri Krainc (also from Massachusetts General Hospital) gave an update on one type of tagging called **acetylation**. Attaching an 'acetyl' tag onto the huntingtin protein may instruct cells to target it for degradation. HDAC4 removes acetyl tags. When Krainc's team made cells without HDAC4, their results suggested that huntingtin removal might be increased. Selisistat, a drug that inhibits the activity of one HDAC enzyme (SIRT1), is being tested in EHDN's PADDINGTON trial. Krainc's team confirmed that Selisistat acts on SIRT1 to increase acetyl-tagging.

Small is beautiful

Complex chemicals are usually not the best drugs, because they are less stable than small molecules, and quite often cannot get into the brain. So, the ideal drug is a small molecule.

One exciting target for small molecule drugs is phosphodiesterase (PDE) inhibition. **Vahri Beaumont** (CHDI) and **Chris Schmidt** (Pfizer) presented the results of their collaborative work. Synapses are the connections that mediate transmission of signals between neurons; PDEs break down some of the signalling molecules at synapses. Because synaptic connections are all-important in the brain, it is hoped that restoring synapse function might improve HD symptoms, or even slow down the degenerative process.

PDE9 and PDE10 seem to be the phosphodiesterases that are most involved in HD pathology. Drugs that inhibit these PDE enzymes restored abnormal electrophysiological changes in mouse brain slices. Tantalizingly, this included improvements in some of the long-term functions that might underlie learning and memory. Pfizer has a plan for human trials of PDE inhibitors. The

timeline for the PDE10 inhibitor studies includes human studies in late 2012 and a 6-month trial in 2013-14. "This is not about rushing headlong into a trial … but a clinical experiment", said Schmidt, "so succeed or fail, we'll learn a lot".

KMO inhibitors were a big HD story in 2011. KMO is an enzyme that alters the balance between a chemical that protects neurons (kynurenic acid) and another that harms them (quinolinic acid). A drug called JM6 was reported to reduce the activity of KMO and enabled HD mice to live longer. **Ladislav Mrzljak** unveiled CHDI's top KMO inhibitor candidate – CHDI-246. So far, it appears to be safe and to produce healthy changes in brain chemistry. CHDI is pressing on with tests of CHDI-246 in three different HD mouse models. Reproducible results are crucial to ensure that only the most promising drugs are tested in human trials.

Novartis has just completed a human trial in HD.

Graham Bilbe described how their drug, Mavoglurant, blocks glutamate receptors and is intended as a treatment for HD symptoms, particularly unwanted movements. The results of the trial should be announced soon.

Getting it right first time

Testing drugs is expensive, so it's desirable to get it right first time. Spearheading the clinical trial efforts from CHDI is **Cristina Sampaio**. As a former member of committees at the European Medicines Agency, Sampaio brings a wealth of expertise to the task. She asserted that we need to move on from approaches that have failed to deliver in the past. We need 'smart' trials, rather than big or long trials.

Sarah Tabrizi (University College London) announced the final data from the TRACK-HD study. TRACK-HD aimed to identify the best combination of biomarkers for testing drugs in HD. Tabrizi demonstrated how the **TRACK-HD** toolkit can tell us how many people are needed for a trial of any drug, and what biomarkers would be best at testing it.

TRACK-HD has identified brain changes that occur long before symptoms emerge in HD. That may sound worrying, but it suggests that the brain is actually good at compensating for damage. As Tabrizi put it, "there's a lot that we may be able to rescue". With this in mind, Tabrizi announced a new study, **TrackOn-HD** that would probe these functional changes in the HD brain before the disease emerges.

Big-picture thinking

Mark Guttman (Centre for Movement Disorders, Ontario) opened a debate on how HD is defined. Does it begin when a neurologist diagnoses it, or is there a 'spectrum' of symptoms that appear gradually over many years? Both patients and doctors are aware of changes that precede an established diagnosis. He suggested that perhaps we need to agree on better language for describing them. A discussion with the global community focussed on this area has begun.

Michael Hayden (University of British Columbia) is looking far ahead. HD may be more common than previously thought. Combine this with an aging population, and HD may become a common disease with many cases occurring in the elderly – something healthcare planners will need to think about.

Finally, your authors gave an update on the first year of **HDBuzz**, now bringing the latest HD research news to the global community in twelve languages.

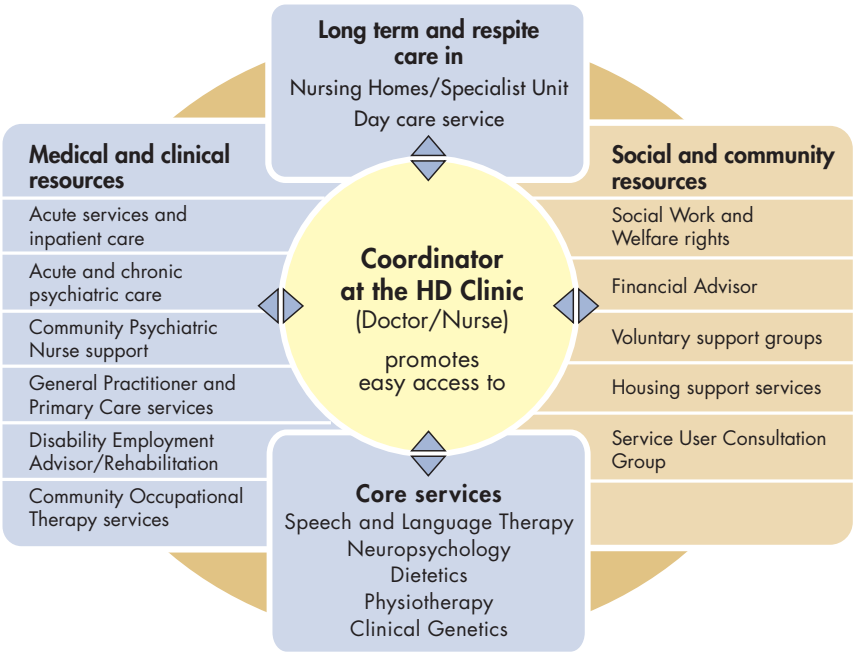
A new era

A new era is beginning in HD drug development, with tailor-made HD therapies poised to be tested in patients. This puts us in a very different place from where we were as recently as five years ago. We have the drugs to test, more in the pipeline, and a clear idea of how to test them.

A Standard of Care in Huntington's disease

Daniela Rae on behalf of the EHDN Standards of Care Working Group and EHDN Physiotherapy Working Group

The complexity of Huntington's disease (HD) and its progression over time mean that individuals with HD require the care of a variety of specialists. To improve quality of life and ensure appropriate long-term management of these individuals, a regular review by a multidisciplinary team is essential (see Figure). It has been recognised that there is little peer-reviewed evidence or systematic guidance for clinicians and other healthcare professionals for the management of this patient group.



The multi-disciplinary Managed Care Network for the management of HD

The Standards of Care Working Group

The European Huntington's Disease Network (EHDN) Standards of Care Working Group (https://www.euro-hd.net/html/network/groups/care) is one of a number of working groups that have been formed to encourage new collaborative work in the care of HD with the aim of developing evidence-based guidelines for best practice. This working group comprises over one hundred clinicians and allied health professionals from various disciplines, such as dietitians, dentists, and speech and language therapists from both Europe and the USA.
The group is closely aligned with the EHDN Physiotherapy Working Group (https://www.euro-hd.net/html/network/groups/physio).
The members of the Standards of Care and Physiotherapy Working Groups have methodically developed clinical guidelines addressing important areas outlined in the Management Care Network and are delighted to announce the publication of a special edition of the Journal of Neurodegenerative Disease Management focusing on Standards of Care for the clinical management of HD.

This unique collection of guidance documents on the management of swallowing, communication, nutrition, dental care, physiotherapy and occupational therapy in Huntington's disease (HD) comprises:

Foreword: ***A standard of care for Huntington's disease: Who, what and why***

Editorial: ***A standard of care for Huntington's disease: A patient and family perspective***

Special Reports:

- Development of physiotherapy guidance and treatment-based classifications for people with Huntington's disease
- Physiotherapy clinical guidelines for Huntington's disease
- Nutritional management of individuals with Huntington's disease: nutritional guidelines
- Oral feeding in Huntington's disease: a guideline document for speech and language therapists
- Management of speech, language and communication difficulties in Huntington's disease
- Guideline for oral healthcare of adults with Huntington's disease
- Development of guidelines for occupational therapy in Huntington's disease

Please follow the link for open access to this series of articles, which is kindly supported by CHDI Foundation: http://www.futuremedicine.com/toc/nmt/2/1

This collection of articles addresses fundamental aspects of the clinical management of Huntington's disease (HD), focusing on non-therapeutic interventions in order to promote uniformity and standardisation of care internationally. Ultimately, it aims to add to the current knowledge on management of HD and would allow practitioners to make informed decisions regarding best patient care.

EHDN Endorsed Clinical Trials

Tim McLean, Clinical Operations Manager of EHDN, West Linton, UK

Overview

Since the last Clinical Trials update in July 2011, there have been successes, frustrations and also a lot of expectations. Some study recruitment targets have been exceeded, whilst other studies have been delayed. Looking to the future, EHDN is undertaking an exciting restructuring of its clinical trials support capabilities, so that it will be well positioned for the expected wave of drug development programmes that are poised to enter the clinic.

This article contains an update on EHDN endorsed clinical trials as well as a brief summary of those under development. These will be featured in more detail in future clinical trials updates.

Trials Recently Completing Patient Recruitment

Recruitment into the **Siena Biotech** sponsored Phase II clinical trial S015-002 of the potential disease-modifying SIRT1 inhibitor, **Selisistat** (SEN0014196), commenced in November 2011. By the end of April 2012, 135 HD patients had been successfully recruited at 12 sites across Germany, Italy and the UK, exceeding the recruitment target nearly 3 months ahead of schedule. This is a tremendous achievement by the project team, site staff and patients involved. Patients have been randomised to receive either Selisistat (at one of two doses), or placebo for a period of 12 weeks. The trial database will be locked for analysis during the third quarter of 2012 following a final round of data monitoring and data cleanup. Depending on the results of this study and other clinical investigations into the safety, efficacy and bioavailability of Selisistat, a much larger global Phase III study may be considered during 2013.

Meanwhile, the **PADDINGTON** study (S015-004), which is co-financed by the European Commission, is in the 'close-out' phase. The database has been locked, and the final report is expected during the second quarter of 2012. This study evaluated two doses of Selisistat and placebo in a total of 55 HD patients across six sites in Germany, Poland and the UK. The primary goal of PADDINGTON was to assess the feasibility of a series of pharmacodynamic readouts that could be used to indicate whether or not Selisistat can modulate its target, and if this delays the progression of HD.

Clinical Trials in the 'Set-up' Phase

Patient recruitment to the **ACTION-HD** study of **bupropion (Elontril®)** for the treatment of apathy in HD patients is scheduled to commence during May 2012. Patients who have been confirmed to be HD gene carriers by the genetic diagnostic test and to exhibit symptoms of apathy as assessed by the Structured Clinical Interview for Apathy Scale will be randomised for treatment with either bupropion or placebo at 4 study centres in Germany. The crossover design of this study requires that after a period of 10 weeks the bupropion dose will be decreased to a 'washout' phase over a 2-week period. The patients then switch treatments, so that those previously on placebo will receive bupriopion and *vice versa* for a further 10 weeks. The four centres are expecting to recruit a total of 40 patients throughout the following year. Recruitment of eligible patients is anticipated to be more challenging for this study than for others because the entry criteria will be more demanding, since each patient will be required to have a caregiver who is willing to be present at all study visits. The primary efficacy assessment will be a change in apathy (as assessed by the caregiver) recorded using the Apathy Evaluation Scale (AES-I). Secondary efficacy variables will include a change in apathy as assessed by the patient and the clinician, changes in motor, cognitive and psychiatric symptoms, and a change in the caregivers distress score using the Neuropsychiatric Inventory (NPI-D). A subset of patients from both treatment arms will also be assessed for changes in striatal and prefrontal activation, as quantified by functional magnetic resonance imaging, in response to a reward paradigm. This clinical trial is led by Professor Josef Priller (Coordinating Investigator) and Dr Harald Gelderblom (Project Coordinator) of the Charité University Hospital, Berlin.

For the **PRIME-HD** study with **Huntexil®** (also known as ACR-16 or pridopidine), protocol development and site feasibility activities have been taking place during the past few months. Following on from the findings of the MermaiHD and HART studies, the sponsor company, **NeuroSearch**, has been in discussion with the Health Authorities of the US (FDA) and of the EU (EMA). Recommendations for the further evaluation of Huntexil® include the investigation of higher doses than were used in the previous two studies. Additional data are also needed to support the previously observed effect on UHDRS-Total Motor Score and to substantiate the clinical relevance of this finding.

The PRIME-HD study is designed to recruit approximately 630 HD patients randomised for twice daily treatment with 45 mg or 67.5 mg Huntexil®, or placebo. The primary study endpoint will be UHDRS-Total Motor Score and, in an attempt to demonstrate the clinical relevance of Huntexil®, patients' overall function will be assessed using the Clinical Global Impression Scale. NeuroSearch has undergone a significant restructuring to focus all of its resources on this development programme and is currently attempting to raise the required funds upon which the initiation of this confirmatory study depends.

Clinical Trials in Development

EHDN has commenced early discussions with a number of pharmaceutical and biotechnology companies with candidate treatments for HD which are currently undergoing pre-clinical development. These include a range of phosphodiesterase inhibitors, most notably PDE10A. In addition, there is a lot of excitement about the potential of gene silencing technologies using **RNA interference** or **antisense oligonucliotides**, although each presents its own drug delivery challenges to ensure they reach their target tissues with minimal unwanted side effects.

Whilst many programmes are at an early stage of development, some may be close to commencing clinical trial set-up by early 2013, and more specific information should be available by the time of the next Clinical Trial Update.

EHDN Clinical Trials Task Force

Following the endorsement of the proposed EHDN Scientific Strategic Plan by the Executive Committee earlier this year, one of the first activities has been to develop and implement the plan for a Clinical Trials Task Force. This Task Force is a committee that will comprise experienced clinical trial investigators and specialists from within and outside the HD research community. Their responsibilities will include (1) overseeing and guiding the activities of a small team of EHDN clinical trial support staff, (2) making recommendations on the overall strategy for clinical trial support services for clinical trial sponsors and participating sites and (3) convening appropriately experienced advisory groups to advise on HD drug development plans. The Task Force held its first meeting in May 2012 and should be well positioned to provide effective support service to the anticipated wave of HD clinical trials.

Test drug	Sponsor	Countries	Centres	Patients (planned)	Recruitment		Status
					Start (planned)	Stop (planned)	
Selisistat (SEN0014196)	Siena Biotech	Germany, Poland, UK	6	55	Complete	Complete	Close-out/ Final reporting
Selisistat (SEN0014196)	Siena Biotech	Germany, Italy, UK	12	135	Nov 2011	April 2012	Recruitment closed
Elontril® (Bupropion)	Investigator lead	Germany	4	(40)	(May 2012)	(Feb 2013)	Set-up/ Start of Recruitment
Huntexil® (pridopedine)	Neuro Search	EU, Latin Am., North Am.	TBC Up to 60	(630)	(2012/13)	TBC	Feasibility/ Site Selection

TBC= To be confirmed

Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy

Scahill RI et al., *Human Brain Mapping* 2011;
doi: 10.1002/hbm.21449, Epub ahead of print

This study demonstrates correlations between brain atrophy and early clinical impairments in Huntington's disease, establishing a link between structure and function.

Background

It is now well known that premanifest Huntington's disease (HD) mutation carriers gradually develop subtle signs and symptoms many years before a clinical diagnosis is established. Functional abnormalities have been observed in different domains, encompassing motor, cognitive and oculomotor function, and neuropsychiatric disturbances. Structural imaging studies have revealed global and regional brain atrophy in premanifest and manifest HD mutation carriers. The present study examined whether or not changes in brain structure correlate with performance in specific clinical assessments.

Subjects and Methods

Brain scans of 239 HD mutation carriers (120 premanifest and 119 early-HD subjects) from the TRACK-HD cohort were obtained using 3-Tesla magnetic resonance imaging. A voxel-based morphometry technique was used to correlate grey and white matter volumes with performance in clinical assessments covering four domains:

1. Quantitative motor: tongue force, metronome tapping and gait
2. Oculomotor: antisaccade error rate
3. Cognitive: recognition of negative emotions, spot the change and the University of Pennsylvania smell identification test
4. Behavioural: apathy, affect and irritability, assessed with the Problem Behaviors Assessment-short version.

Results

Significant correlations between task performance and brain atrophy in different areas of grey and white matter were found for the endpoints of tongue force, metronome tapping, antisaccade error rate and negative emotion recognition (see table). For instance, deficits in tongue force coordination were associated with atrophy not only in the striatum, but also in other motor and sensory areas (see figure). By contrast, there was little evidence to relate gait and the other cognitive and behavioural measures that were tested to structural brain loss.

Endpoint	Grey matter changes	White matter changes
Tongue force	L/R caudate R precentral gyrus R cuneus L/R precuneus	L/R occipital lobe R internal capsule Splenium corpus callosum L frontal lobe
Metronome tapping	L/R putamen	L/R internal capsule R external capsule
Antisaccade error rate	L/R caudate L lateral occipital gyrus R superior temporal gyrus L putamen R inferior frontal gyrus	L external capsule L/R internal capsule R occipital lobe L parietal lobe R frontal lobe
Negative emotion recognition	L precentral gyrus R precuneus R cuneus L/R lingual gyrus	L external capsule R parietal lobe R superior frontal lobe R inferior parietal lobe

L=left, R=right

Conclusions

This work reveals new and specific associations between structural brain loss and clinical impairment in HD. This yields insights into functional correlates of the global and regional brain atrophy observed in prodromal and early HD, with a view to improving our basic understanding of the regional functionality of different brain areas in disease onset and progression.

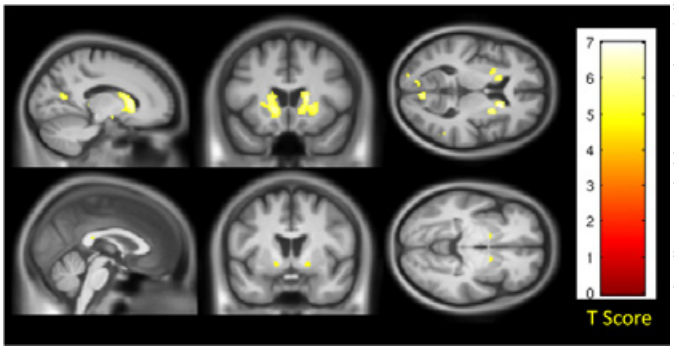


Figure kindly provided by Rachael Scahill

Statistical parametric map showing correlations between increased variability in tongue force and reduction in grey matter (top) and white matter (bottom), highlighted in yellow.

Summary by Diana Raffelsbauer, Freelance Medical Writer, PharmaWrite, Germany
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Potent and selective antisense oligonucleotides targeting single-nucleotide polymorphisms in the Huntington disease gene / allele-specific silencing of mutant huntingtin

Carroll JB, Warby SC et al., *Molecular Therapy* 2011; 19: 2178-85

This study describes the first experiments using antisense oligonucleotides to show that mutant huntingtin can be specifically switched off *in vitro* and *in vivo*.

Background

Mutant huntingtin causes the dysfunction and death of neurones, but normal or wild-type huntingtin is essential for embryonic development and proper brain function. Therefore, research has recently focused on strategies to specifically prevent mutant huntingtin from being made, for instance by selectively 'silencing' (switching off) the mutant *HTT* gene. For this purpose, it is possible to take advantage of variations in the DNA sequence between different individuals – single-nucleotide polymorphisms (SNPs) – some of which occur in the *HTT* gene.

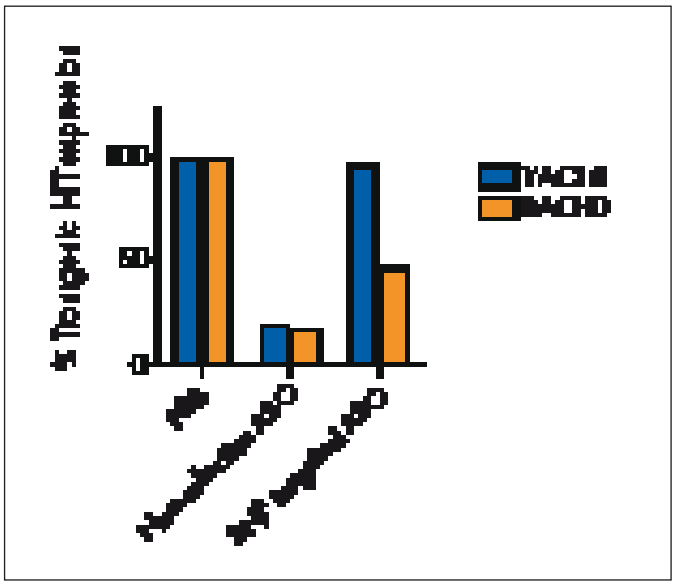
The authors of this paper used antisense oligonucleotides (ASOs) to *HTT*. These ASOs are short, synthetic, single strands of RNA that are complementary to the *HTT* messenger RNA (mRNA). ASOs bind to mRNA in the cell nucleus causing the target mRNA to be degraded, so that it is no longer available to be translated into protein. Importantly, ASOs can be designed so that they discriminate between the SNP variation in the DNA between different people. Therefore, if an HD mutation carrier has a different DNA sequence at a SNP on their mutant *HTT* and wild-type *HTT* genes, it might be possible to cause the degradation of the mRNA made from the mutant gene whilst leaving the wild-type-mRNA intact. This is an exciting possibility because ASOs can be delivered to different cell types in the brain via infusion and do not require the use of viruses as delivery system.

Results

Carroll et al. looked at the DNA of 234 HD patients and identified 50 SNPs within *HTT* that were associated with the CAG expansion and that could be potentially used for silencing the mutant *HTT* gene. In collaboration with ISIS Pharmaceuticals (Carlsbad, USA), they synthesised 48 ASOs that targeted these SNPs. They tested them in skin cell cultures derived from HD patients. This initial screen identified 19 ASOs targeting 14 SNPs that effectively reduced the mutant *HTT* mRNA. These ASOs were then prioritised according to their potency, selectivity and dose-response profile. The top four ranked ASOs were further examined in cultured neuronal cells derived from the YAC128 and BACHD mouse models. The observed reduction in mutant huntingtin levels was dose-dependent and varied from 39% to 68% at the highest dose tested. One of the ASOs was chemically modified to improve potency and injected into the striatum of BACHD and YAC18 mice. This ASO reduced the amount of mutant huntingtin in the mouse brain by nearly 50% (see figure).

Conclusions

The authors demonstrated that potent and selective silencing of the mutant *HTT* gene can be achieved both in cells and in mice using ASOs targeting a few SNPs that are clinically relevant for the human HD population. This is the first step in what will be an iterative process to build a panel of ASOs that are tailored at the individual genotypes of people carrying the HD mutation.



The YAC18 and BACHD mouse models express human HTT transgenes that differ at a SNP. Administration of a non-selective ASO decreased HTT levels in both the BACHD and YAC18 models. The targeted ASO detects the SNP sequence that is present in HTT in BACHD but not YAC18 mice; thus its administration selectively decreases BACHD HTT levels.

Upcoming Meetings 2012/2013

June 8-10	27th Annual National Convention of the Huntington's Disease Society of America, Las Vegas, NV, USA http://www.hdsa.org/national-convention/convention
June 9	Meeting of the Huntington's Disease Association of Ireland http://www.huntingtons.ie
June 9-12	22nd Meeting of the European Neurological Society, Prague, Czech Republic http://www.congrex.ch/ens2012
June 17-21	16th International Congress of Parkinson's Disease and Movement Disorders, Dublin, Ireland http://www.mdscongress2012.org/
June 21-24	Meeting of young adults from HD-affected families in Spain, Burgos, Spain http://www.euro-hd.net/html/network/news
June 23	Meeting of the Austrian Huntington Association, Salzburg, Austria http://www.huntington.at/
June 23-26	European Human Genetics Conference 2012, Nurnberg, Germany https://www.eshg.org/eshg2012.0.html
Sept 8-11	16th Congress of the European Federation of Neurological Societies (EFNS), Stockholm, Sweden http://www2.kenes.com/efns/pages/home.aspx
Sept 14-16	EHDN 2012, 7th EHDN Plenary Meeting, Stockholm, Sweden http://www.euro-hd.net/html/ehdn2012
Oct 4-6	22nd Alzheimer Europe Conference, Vienna, Austria http://www.alzheimer-europe.org/Conferences/Vienna-2012
Oct 12-14	Annual General Meeting and Family Conference of the HD Association of England and Wales http://hda.org.uk
Oct 13-17	25th Congress of the European College of Neuropsychopharmacology, Vienna, Austria http://www.ecnp.eu/en/Congress2012/ECNP%20Congress.aspx
Oct 13-17	Neuroscience 2012, Annual Meeting of the Society for Neuroscience, New Orleans, LA, USA http://www.sfn.org/index.aspx?pagename=annualmeeting
Oct 19-21	Annual General Meeting of the German Huntington Association, Oberwesel, Germany http://www.huntington-hilfe.de/
Oct 19-21	Meeting of HD-affected families in Spain, Centro CREER, Burgos, Spain http://www.euro-hd.net/html/network/news
Oct 24-27	EANS 2012, 15th Congress of the European Association of Neurosurgical Societies, Bratislava, Slovakia http://www2.kenes.com/eans/Pages/Home.aspx
Nov 6-10	62nd Annual Meeting of the American Society of Human Genetics, San Francisco, CA, USA http://www.ashg.org/2012meeting/
Nov 8-10	2nd International Congress on Neurology and Epidemiology, Nice, France http://www.neuro-conference.com/2012/
Nov 10	6th Annual Huntington Disease Clinical Research Symposium, Seattle, WA, USA http://www.huntington-study-group.org

2013	
Jan 25-27	5th European Neurological Conference on Clinical Practices, Krakow, Poland http://www.enccp.net/
Mar 6-10	11th International Conference on Alzheimer's and Parkinson's Diseases, Florence, Italy http://www2.kenes.com/adpd/Pages/Home.aspx
Apr 11-14	7th World Congress on Controversies in Neurology, Istanbul, Turkey http://comtecmed.com/cony/2013/
Sept 22-27	21st World Congress of Neurology, Vienna, Austria http://www.xeniosworld.com/meeting-services/austria/austria-vienna/vienna-lands-2013-world-congress-of-neurology/
Oct 17-20	8th International Congress on Vascular Dementia and 1st Cognitive Impairment European Meeting, Athens, Greece http://www2.kenes.com/Vascular/Pages/home.aspx

This is the last edition of the EHDN Newsletter to be edited by this team. Gill and Jenny would like to say a particular thank you to the other members of the editorial team for their sterling efforts in producing the newsletter, and to all the people who have contributed articles over the last 4 years.